The Journal of
NERVOUS and MENTAL DISEASE

VOL. 129, NO. 6
December, 1959
SERIAL NO. 925

A REVIEW OF SOVIET RESEARCH ON THE CENTRAL NERVOUS SYSTEM EFFECTS OF IONIZING RADIATIONS

WALTER R. STAHL, M.D.[1]

INTRODUCTION

Our knowledge of Soviet research and theory on the biological effects of ionizing radiations, based on available Russian literature and presentations at scientific conferences, reveals a general agreement between the scientists of the West and the USSR on somatic radiation effects, except in regard to the radiosensitivity of the central nervous system (CNS). The Soviets have strongly and repeatedly stressed that the CNS must be considered as being moderately or highly sensitive to radiation. They have implicated the CNS in the pathogenesis of all types of radiation injuries and done a great deal of experimentation stressing the role of the CNS in radiation pathology.

Before undertaking a detailed consideration of the pertinent research work, it is perhaps interesting to note the conceptual basis for the above viewpoint. Soviet physiological theory and experiment is largely centered about Pavolian "nervism." Very briefly this theory may be interpreted to mean that the CNS exerts a controlling influence over all types of reactions in the organism, including various local tissue responses such as inflammation, hypertrophy, etc. Wholly local, or non-nervous, reactions on the part of tissues and organs are considered, at best, as being of only secondary importance because of the basic controlling role of the CNS in the whole organism. Thus, in considering radiation pathogenesis Soviet physiologists have persistently sought the CNS mechanisms that might be responsible in phenomena as, for example, post-radiation pancytopenia.

In addition, the development of such CNS control is accepted as being part of the "evolutionary adaptive" process. There appear to be various viewpoints among Soviet scientists on whether reactions to radiation also have an evolutionary basis and on the question of adaptation to radiation.

Very few of the materials covered by this review are available in translation. Some of the references are reported second-hand from a comprehensive review on CNS effects of radiation by N. N. Livshits (45). A number of Livshits' references have been reproduced in the bibliography with the thought that certain of them become available in the U.S. in the future, though not known to be obtainable now. All of the more recent articles have been read in the original and are catalogued at the National Library of Medicine, where further inquiry should be made about availability of copies and possible translations.

The critical reader and especially the neurophysiologist will doubtless be dissatisfied with some of the descriptions of experiments which follow. In the large majority of cases this is due to deficiencies in the original materials; a critical discussion of

[1] Science Research Institute, Oregon State College, Corvallis, Oregon. The author wishes to express his sincere thanks for the valuable guidance and assistance of Clinton C. Powell, M.D., N.I.H., Donald R. Chadwick, M.D., Division of Radiological Health, U.S.P.H.S. and Scott Adams, N.S.F.

the reviewed experiments is provided in the concluding portion of this review. There is also some problem of terminology (though not of translation). For example, the Russians appear to use the term "chronaxie" in a wider sense than commonly accepted in this country. They apparently apply it to any stimulation-response curve, including that for an entire nerve tract or even muscle. Since the reviewer is a radiobiologist he has chosen to repeat the Russian usage at face value, without extensive attempts at interpretation. The descriptions of conditioned reflex experiments appear particularly obscure in some cases. In addition, the bulk of material covered precludes very detailed presentation of experimental techniques. However, every effort has been made to provide enough data to allow the interested researcher to initiate similar, if perhaps not exactly identical, experiments.

It is hoped that this review will serve to outline in a general way the scope of Russian research on CNS effects of radiation and lead to an expansion of work in this important area.

MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS IN THE CNS RESULTING FROM IRRADIATION

The Soviet conclusions on morphological changes in the *adult* CNS following irradiation are generally similar to those of the West, and on the basis of the majority of the papers reviewed, a threshold for microscopic changes may be set at approximately 1000–2000 r. There appears to be no unanimity among Russian researchers as to whether vascular or direct neuronal injury takes place (38).

Specifically, L. F. Semenov (64) failed to find histological changes in the cerebrum of rats and mice after roentgen exposures of 1300–1400 r. Ya. Ye. Shapiro (66) gave dogs a total of 2500–4000 r, using 6 × 8 cm fields bitemporally over a period of 10–12 days, and found severe diffuse degenerative changes, most pronounced in the midbrain. I. M. Zhdanov (72) studied nerve elements in the heart and cervical sympathetic ganglia of rabbits, using total doses of 900–1500 r, and found no evidence of neuronal injury. E. F. Galkovskaya (16) studied the spinal cord of the axolotl (Salamander) at 1–43 days after doses of 10,000 and 20,000 r and found no changes below 20,000 r.

Lebedinsky (38) has commented on the unevenness of radiation alterations in the CNS of mammals. Such changes are stated to be more marked in the cortex, red nuclei, pontine nuclei and spinal cord; lesser changes are seen in the subcortical region, subthalamic nuclei, cerebellum and some stem structures. He also notes a histological unevenness of response, as shown by histochemical methods based on ribonucleic acid content.

Livshits (45) notes Western data placing a threshold for histological changes at 1500 to 10,000 r without comment but stresses that functional alterations nonetheless occur at much lower doses.

Recently (1957), however, pathomorphological effects from 50–250 r doses of x-rays on the CNS in white rats were reported by M. M. Aleksandrovskaya (1). Using histochemical methods it was concluded that doses of 50–150 r produced reversible alterations in nervous elements while 250 r could result in irreversible destructive changes. This author indicates that the above changes were the result of direct radiation effects on the parenchyma since vascular structures showed much less response.

In addition, T. N. Oleynikova (61) describes changes in mammalian peripheral nerve fibers after exposure to P-32 internally, application of P-32 to the skin and x-irradiation in a dose of 900 r. Degenerative changes in nerve fibers were found in all cases, apparent sometimes as early as 30 minutes after irradiation, and lasting up to a year. Local applications resulted not only in local nerve fiber damage but

also in alterations of other peripheral nerves in the organism.

In regard to the young CNS, there is also essential agreement. Yu. M. Olenov and A. D. Pushintsyna (60) reported in 1952 on the roentgen irradiation of pregnant mice. Doses of 240–750 r produced notable damage to the fetal CNS and the threshold for this effect histologically was set at 80 r. In a previous paper by Olenov (59) it was claimed that histological changes were visible in newborn mice following 40 r. D. G. Shefer (67) irradiated pups with 4–5 erythema doses and found neuronal alterations in the cortex and subcortical formations of the midbrain, with lesser changes in the stem and cerebellum. The same doses in adult dogs produced no histological changes. Livshits notes that Soviet work on young animals is in basic agreement with that of Hicks and others.

A number of Russian papers deal with radiation-induced alterations of spinal reflexes which are interpreted as an indication of functional changes in the spinal cord. Quite a few of the older papers using this approach relied on radon capsules as a radiation source and no accurate statement of dose is given; most of these will be passed over. Ye. I. Bakin (5) irradiated frogs with radon preparations and concluded (in 1956) that the tremors occurring after sizable doses were due to disturbances in the sensory tracts of the spinal cord, which he found to be considerably more sensitive than motor tracts.

S. A. Lifshits (39) also studied the effects of roentgen irradiation of the spinal cord of the frog on the "sensory" and "motor chronaxie" of muscle in the frog. Radon capsules were used and calculated doses are given. Doses up to 4500 r had no effect on these parameters, while 6000 r resulted in a temporary rise of "sensory chronaxie" of ten times, with a return to normal in 2–4 days. No changes were found in "motor chronaxie" nor were such alterations observed following irradiation of the extremities.

Alterations in spinal reflexes after doses of 500–1000 r in the rabbit have been observed by Z. M. Gvozdikova (25). The whole-body, specific spinal centers and corresponding receptor skin zones were irradiated individually. Unconditioned motor reflexes were depressed in all instances, but 1000 r doses seemed to have a greater effect on spinal centers while 500 r exerted more influence via pathological reflex stimulation from the periphery. With whole-body irradiation both effects are implicated.

In a very recent work (1958), A. I. Ul'yanova and V. P. Shmelev (70) reported on the effects of radioactive bromine on the "chronaxie" of the hip muscle and hip withdrawal reflex in the dog. Seven dogs were given 0.17 to 0.34 millicuries of Br-82 one to four times. The "reflex chronaxie" showed a lengthening in most cases to values 135–320 per cent of normal, appearing in minutes to 27 hours. In several experiments a shortening of the chronaxie was observed at certain times, but this was felt to be inconstant. Presented data strongly suggests an increased chronaxie. The chronaxie of the muscle also changed, with a brief initial decrease followed by an increase, all occurring within a few hours. Normality was usually reestablished by 24 hours, while the reflex chronaxie alteration lasted up to 5 days, suggesting at least two sites of action. An exact mechanism is not proposed.

Yu. K. Kudritskiy (33) has reported on the response time for the knee flexor reflex in the rabbit, as influenced by chronic whole body irradiation at the rate of 10 r per day. A slowing of the response by a factor of 2–10 times was first noted at about the 25th day and lasted until the 120th day, when there was an apparent return to normal that persisted up to 200 days, at which point the experiment was terminated. In rabbits receiving 100 r per day there is a slowing of response followed again by a return to normal during the period of the

3rd to 8th days, and then another slowing lasting until death. A single dose of 10 r, however, is stated to cause a considerable increase in response time (by a maximum of four times) with a peak at about 10 days. A second dose of 10 r given subsequently has much less effect. Both this phenomena, and the return to normal noted above, are interpreted as being strong evidence for adaptation on the part of the CNS to radiation effects. Commenting on similar work, Lebedinsky states that a significant increase in response time was observed with only 0.1 r.

In another paper on knee flexor reflexes, Kudritskiy has also reported (34) on the response to a standard dose following preliminary irradiation. Rabbits given 0.1–0.5, 10 and 100 r per day chronically or several large doses of hundreds of r, showed a common response in that the deviations from normal in the knee flexor reflex timing after 10 r were restituted more quickly. This was interpreted as showing an *adaptive* reaction on the part of the CNS.

I. V. Fedorova (14) studied the effects of 10 r of whole-body, hard x-radiation on the latent period of the rabbit knee flexor reflex, in what appears to be a careful experiment done under Kudritskiy's supervision. Twenty animals were used with seven controls, chosen in an unstated manner. The parameter studied was the *variability* of the reflex latent period. An electronic millisecond (msec.) stopwatch was used, with automatic registration of the 0.5–1.0 volt, 6 microsec. stimulating pulse and onset of significant motion in the leg. A mechanical load of 100 grams was placed on the limb to give a more uniform response. Needle electrodes, 5 mm apart, were implanted subcutaneously over the knee and special care was taken to avoid errors due to the associated local inflammation.

The author felt satisfied with control data showing a normal latent period of about 150–168 msec., with an average variability of 7–9 msec. and range of only 2–18 msec. Forty-three trials were done on the irradiated animals. It was found that the variability (but apparently not the average latent period itself) of the knee flexor reflex was greatly increased during the first 8–10 post-irradiation days. In most animals the variability of the latent period was 10–60 msec. and in individual trials it reached several hundred msec. At later times the findings were less striking. It was concluded that this greater inconstancy of response was a CNS radiation effect, at an unspecified site.

In 1956 N. K. Poplavskiy (63) presented some intriguing data on spinal responses in mice following irradiation carried out during different seasons of the year. The response studied was muscular activity resulting from skin stimulation at an audio frequency using a variable voltage (5–15 volts). After 40, 80, 160, or 320 r, during the spring, there was an apparent decline in reflex activity the first 8 hours after irradiation. In the fall, however, the same doses produced an increase in reflex activity lasting about 24 hours. Normality was restored in 1–2 days in all cases. Doses of 720 and 1440 r produced a decline of activity followed by a return to normal that persisted until death. It is concluded that reflexes involve a seasonal cyclic component of some sort.

Lebedinsky (38) mentions changes in electroretinograms following irradiation of the anterior chamber of the rabbit eye with Cobalt-60. Such changes are discernible at 2500–3000 r and marked with 4000–6000 r. The reviewed Soviet works show no unanimity on the causes for alterations in neuronal or nerve fiber function. Direct irradiation effects, metabolic alterations and toxic effects are mentioned by various authors as possible factors.

Alterations in afferent impulses to the CNS resulting from irradiation may be stressed as one major point in current Soviet theory in this field. One surprising claim, that Livshits notes has never been duplicated, was made by K. Kh. Kekcheyev *et al.* (27). He described an increase in the

threshold of the eye in the human to light perception following roentgen irradiation of the fingers in doses of only 30–100 r.

M. N. Livanov (41) recently reported on the results of local irradiations of the plantar nerve of the rabbit with doses of 500–1000 r. This dose was found to increase the action currents associated with a standard tactile stimulation of the foot for 1–2 days; subsequently they were subnormal and then recovered. Doses of 3000–5000 r produced a sharp decline in action currents with a slow recovery. Livanov feels that the changes are due to an altered physiochemical environment and result in an abnormal afferent flow to the CNS.

N. S. Delitsina (8) also reports on studies of nerve action currents after irradiation in the rabbit (27 animals). Recordings were made of potentials in the plantar nerve of the paw after local irradiation with 500–1000 r. Spontaneous discharges were observed immediately after radiation and there were prolonged unstable alterations in response to tactile stimuli. In cats (24 animals) action currents were measured in an abdominal nerve after 500 r whole-body irradiation. It was found that the radiation resulted in a sharp decrease in amplitude and increase in frequency of currents. Rabbits (40 animals) were also given single doses of 500 and 1000 r whole-body, and EEG studies made on the cortical response to stimulation of the rectum. It is stated that after irradiation the response was depressed for 2–3 days and then became unstable with evidence of cortical inhibition due to excessive afferent activity.

One area in which the Soviet literature contains a considerable amount of data is the effects of radiation on the electroencephalogram (EEG). M. N. Livanov has done much work in this field and stresses the phasic[2] nature of the changes in the EEG following whole-body irradiation of mammals with 500–1000 r. Generally he notes an immediate increase in bioelectric potentials, with lowering of sensory thresholds, followed by a decrease in activity after about 30–60 minutes. The depression of EEG activity reaches a maximum at 18–20 hours. After 48 hours spontaneous activity recovers but responses to stimuli are irregular and unpredictable.

In another report Livanov (43) has detailed the course of events in the brain of the rabbit after 1000 r as follows. Immediately after irradiation there is an increased flow of impulses to the brain with an associated inhibition of spinal centers. The cortex and subcortical centers show increased excitability for some hours. At the end of about 24 hours the cortical excitability is replaced by profound depression; the excitability of the subcortical centers continues to increase and the spinal reflexes remain inhibited. Over 2–3 days the inhibitory state of the cortex disappears while the subcortical abnormalities continue to increase. Spinal reflexes show some return to normal. Livanov feels that death from radiation sickness involves profound derangements of centers in the brain stem, with temporary acute vagotonia in the terminal period.

In a recent (1958) paper, M. N. Livanov and L. I. Kaburneyeva (42) report on the use of rather small doses of novocaine to curtail the afferent overactivity noted above, in the attempt to prevent pathological malfunction in the CNS. Thirteen pairs of adult rabbits were used and recordings made with a standard EEG lead and from an electrode placed over the dura mater in the parietal region via a trephined opening. The results were interpreted as showing increased cortical sensory inflow. These animals were irradiated with 1000 r of hard x-rays given in about 30 minutes. It is noted in this paper that irradiated controls show significantly increased cortical bioelectrical activity at about 40–60 minutes, with a possible second increase at 2 hours; then there

[2] This word is frequently encountered in the Soviet physiological literature and refers to phenomena characterized by several irregular oscillations with a later trend toward normal values.

is a decline to minimum at about 24 hours, followed by recovery.

Novocaine was tried in various amounts, with injection through an ear vein. The following treatment regime is given as optimal: two cc of 1 per cent solution immediately after irradiation; 1 cc at 2 hours; then 2 cc daily for 7 days. The authors state that with this treatment the animals showed less change in cortical bioelectric activity, fewer gastro-intestinal disturbances, less weight loss, decreased depiliation and greater activity. At a dose level of 1000 r almost half of the treated animals survived while all of the untreated controls died. Novocaine treatment was found to be effective against irradiation of the body with the head shielded, but not protective when the head alone was exposed to 3000 r. A representative tracing is given for a rabbit that was given 1000 r and novocaine at 40 minutes, but unfortunately there are no control tracings without novocaine treatment. Further material on novocaine therapy of radiation sickness is quoted below in the section on the acute radiation syndrome.

Yu. G. Grigor'yev (23) reports in 1954 on EEG responses in patients receiving radiotherapy from a Co-60 teletherapy unit. Most of the treatments consisted of 50–100 r administered to a small portion of the head at a rate of about 7 r a minute. An effect on the EEG was observed immediately and consisted of an initial increase usually followed by a depression within minutes to hours. This effect appears to be more pronounced in the irradiated region, as shown by local EEG leads. However, in this work and in some other studies using the EEG, there is no mention of controls to assess possible patient excitement when the unit is turned on—with later relaxation or even sleep; neither is previous drug administration mentioned. These factors are pertinent to the observation that the above response seems to decline in subsequent therapy sessions and may disappear as early as the 4th treatment. The same reaction is also stated to occur during irradiation of other parts of the body.

Ya. I. Geynisman and Ye. A. Zhirmunskaya (19) made EEG observations on patients undergoing irradiation of the carotid sinuses because of hypertension (this is apparently a fairly widely-used technique in the USSR). Total doses of 160–320 r (40–80 per session) were given to the carotid area; field size is not stated. In some cases the cortical temporal lobes were radiated alternately with the carotid sinuses, using the same total doses. Following irradiation there appeared to be a decrease in spontaneous cortical biocurrents and excitability, which is stated to result from "negative induction from subcortical nerve structures".

Lebedinsky (38) comments on the above work. In addition he mentions studies of the rabbit cortex using a multiple pick-up and amplifier system with "mosaic" representation on a special instrument developed by Livanov and Ananiev. This device displays a number of cortical biopotentials simultaneously on a light panel. Details are not given in the available materials. Following a single dose of 1000 r in the rabbit, "The cortical mosaic appears more pronounced, subsequently becoming weaker for a long time (24 hours or more). . . .". Simultaneous electrical measurements have been made of cortical and spinal motor areas and the cortical activity was found to recover first after irradiation. Livanov (40) conducted some detailed experiments on the passage of impulses from the retina to the cortex, through the intermediary nerve formations, and found that, 30–60 minutes after irradiation of the rabbit with 500–1000 r, there was an increase in cortical biocurrents and lowering of light threshold. Within a few hours cortical activity fell to below normal and minimum occurred at about 24 hours. It is claimed that in part the latter is due to inhibition in the subcortical formations.

Soviet neurophysiologists are accustomed

to using test doses of such agents as caffein and bromides to assess CNS activity. Using this technique, in human therapy patients who received total doses of 2000 r, caffein was found to produce unusual reactions, suggesting that the nerve cells had decreased work-capacity and ceased to function normally because of over-stimulation (38).

The above work on bioelectrical phenomena has been widely quoted by the Russians as a proof that CNS effects occur at all radiation levels and play an important part in radiation pathophysiology.

CENTRAL NERVOUS SYSTEM ROLE IN ACUTE RADIATION SYNDROME

Livshits (45) and others often stress that in the West the concept of a low radiosensitivity on the part of the CNS has led to insufficient study of the role of the CNS in the acute radiation syndrome. It is pointed out, for instance, that CNS changes were analyzed only in a limited way in the accidental cases of substantial radiation exposure reported by Hempleman *et al.*

However, there is no unanimity among Russian researchers on the manner of CNS participation in the acute radiation syndrome. Various authors cite the following mechanisms as being of possible significance: 1) specific or non-specific stimulation of receptors or nerves resulting in an abnormal afferent flow to the CNS; 2) direct effects on the CNS causing disturbances of activity in all its parts; 3) disturbances of conditioned reflex (CR) activity; 4) upsets in autonomic coordination; 5) indirect disturbances of the CNS in all its parts by circulating toxins and metabolites; 6) disturbances in "trophic control" of various tissues by the CNS.

At the All-Union Conference on Medical Radiobiology, held early in 1956, L. A. Orbeli, who is quoted by Livanov (40), presented a rather moderate view in a paper on the pathogenesis of the radiation syndrome. He indicated that it was impossible, at that time, to determine whether CNS disturbances were primary or the result of changes in other organs and tissues of the body. Significantly, he stated that no evidence was available to prove specific effects on receptors resulting from tissue radiation injuries. He noted that nothing unique could be detected in the noted CR alterations and that they were similar to those occurring with toxic agents. He observed that the early development of certain CR changes does not prove that they determine the course of the subsequent radiation syndrome. At the same meeting P. D. Gorizontov (21) stressed the importance of toxemic factors and hematological disorders in the acute radiation syndrome, without emphasizing the importance of the CNS.

The statements above represent a considerable moderation of view compared to earlier writings. However, it is still maintained by Orbeli that disorders of CNS activity can be detected by the CR method when no symptoms of the radiation syndrome are present. A. V. Kozlova (31) stresses that CNS alterations are one of the most significant results of chronic low-level irradiation. She feels that subjective manifestations of these alterations include increased fatigableness, irritability, headaches, loss of attentiveness and forgetfulness.

M. N. Livanov (41) reviewed in 1956 the clinical data on accidental exposures in the USSR and elsewhere. He lists weakness, dizziness, fatigue and anorexia in near lethal exposures, but notes no specific reflex alterations in humans suffering accidental exposures. In some of the above Soviet cases considerable attention was apparently given to a careful CNS appraisal.

V. I. Kuznetsov and twelve other authors (35) report clinical observations on a number of individuals exposed to radiation at 5–10 times the usual maximum permissible limits over long periods of time, under circumstances not stated. In regard to CNS function they noted "functional, asthenic disturbances" with or without objective

alterations such as polyneuritis, polymyositis and evidence of CNS vascular deficiency. Other pathology observed included atrophic-nonsecretory states of the nasopharynx, hypotonia, bradycardia, enlargement of the left ventricle, and the expected hematopoietic and general atrophic manifestations of chronic radiation sickness.

Ye. I. Antipenko (3) reporting at a USSR. Academy of Medical Sciences Conference held in late 1956, made use of experimental neuroses in dogs to investigate the long-term effects of an acute radiation exposure. He found deviations from normal in regard to vascular phenomena, blood pressure, general behavior, etc., for three or more years after a single acute exposure. In another paper Antipenko (2) reports that dogs surviving 650 r of Co^{60} gamma-rays and subjected to an experimental neurosis ("conflicting CR method of Kurtsin") show a depressed leucocyte count and other evidence of late radiation effects after this form of secondary stress.

Lebedinsky (38) discusses the role of the endocrine system in the acute radiation syndrome and states that there is an increase of thyroid activity after radiation. Thiouracil pretreatment and cervical sympathetic blockage by novocaine are said to result in lessened hypermetabolism, suggesting stimulation of the thyroid via nervous routes; a hypophyseal mechanism is not excluded, however. In general, endocrine reactions are accepted by Lebedinsky as being an important mechanism in the pathogenesis of radiation syndrome, and are considered to be part of an adaptive response.

The role of physical stress in radiation sickness has been discussed by L. N. Ugodskaya (69). It is reported that rats given 750 r of x-rays show a better survival after being subjected to physical stress prior to radiation. Changes in the hemopoietic organs occur earlier in this group but they also seem to show an earlier recovery.

As early as 1933 S. A. Nikitin and Ye. P. Maksimchuk (58) reported on the occurrence of "roentgen shock," involving phases with excitement, depression, tremors and incontinence, followed by death in 45–90 minutes, after doses of 2000–2700 r in small mammals. The initial acute reaction could be prevented with ether, chloroform or magnesium sulfate narcosis; with this treatment animals that would have died promptly survived for 4–8 days. Livshits (45) cites various reports demonstrating the beneficial effects of sedation in roentgentherapy. A. N. Kruglov and I. M. Klavdiyenko (32) note that early radiation reactions can be prevented by phenobarbital pretreatment. B. G. Mikhaylovskiy (50) reports that camphorated hyoscyamine and camphorated scopolamine have a favorable effect on the course of radiation sickness.

It has been claimed by L. F. Semenov (65) that a combination of adrenaline and acetylcholine given directly before irradiation has a distinct protective effect in mice, which exceeds that due to cysteamine, cystamine and thiourea. A. A. Gorodetskiy (22) found that phenamine (2.4 mg/kg) produced a worsening of radiation sickness following 800 r in mice and 900 r in rats, when given prior to irradiation. A smaller dose (0.05 mg/kg) administered before irradiation appeared to be slightly beneficial as a form of prophylaxis, but no statistical corroboration is given. In earlier work, D. Lapitskiy (36) found strychnine to be protective for frogs given 0.5 to 1.5 erythema doses of x-rays.

A recent (1958) and interesting work of this type is a paper by S. P. Sizenko and V. V. Markevich (68) on the therapeutic value of parenteral novocaine administered at various times before and after irradiation. Studies were done on adult rabbits given 1000 r of either gamma or hard x-rays. Novocaine was administered in a dose of either 0.1 g/kg or 0.03 g/kg, but the smaller dose turned out to be largely ineffective. The drug was injected via an ear vein 20–30 minutes before irradiation (10 animals), 15–20 minutes after irradiation

(5), and 72 hours post-irradiation (5); 10 controls were irradiated but not treated with novocaine. All groups had similar early post-irradiation courses, but later the animals receiving preliminary novocaine treatment showed a distinctly improved course with less depression, better appetite, and decreased weight loss. Two out of ten animals in this group died while in the three other groups 70–100 per cent died. It is concluded that use of novocaine in a quantity of 0.1 g (dry) per kilogram exerts a protective effect because of suppression of abnormal afferent inflow to the CNS.

L. A. Dimitrov (9) cites data suggesting that Co^{60} pretreatment some time prior to general irradiation has a protective effect because of an adaptive reaction. Experiments were done on 12 dogs, 8 of whom served as controls and were exposed to 800 or 2000 r. The remaining four animals were given 3.3 to 7.3 microcuries per kg. and two weeks later exposed to 2000 r (3 dogs) or 800 r (one dog) doses. It is stated that all of the latter animals survived while all the controls died and also that the animals receiving preliminary Co^{60} had radiation syndromes of decreased severity. An adaptive reaction is discussed.

THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN RADIATION REACTIONS

Livshits (45) presents a variety of data on this problem and seems to conclude that the autonomic nervous system plays an important role in certain radiation reactions, though its significance is no greater than the CNS in general.

Certain studies have been made on the effects of radiating regions containing autonomic structures. Ya. I. Geynisman and Ye. A. Zhirmunskaya (18) irradiated the paravertebral sympathetic chains in frogs (field size not stated). Following doses of 5400 r they noted a decline in the electrical activity of sensory nerves in response to skin stimulation, which was thought to be mediated by the autonomic nervous system.

I. P. Dolgachev carried out a number of experiments on the irradiation of cervical sympathetic ganglia with radium sources. In one paper (10) he found that high doses to these structures in rabbits resulted in pneumonias; this reaction was not influenced by transsection of the post-ganglionic nerves or vagus nerve branches to the nodose ganglion. However, radiation after section of the spinal cord below the thoracic level was not associated with pneumonias. In his Geneva paper, Lebedinsky (38) also reported on work by the above author, which showed that 3–10 hours after cervical irradiation rabbits demonstrated ocular reactions indicative of sympathetic stimulation; at 1–2 days there was a stasis in auricular vessels, contraction of the pupils and pneumonia (dose is not stated).

A. N. Gamelaya (17) *et al.* investigated the effect of cervico-sympatho-vago blocks in the course of irradiation sickness in dogs given 600–700 r. The block was accomplished with novocaine, beginning at 3–4 hours after irradiation, and using alternate sides every second day; bilateral blocks were not attempted. With the general course and leucocyte count as criteria, the above procedure had no beneficial effect and apparently several animals died during the blocking procedure.

M. A. Movsesyan *et al.* (51) state that local irradiation of the cervical sympathetic ganglia in rabbits with doses of 100 r (details of radiation conditions not given) results in hyperglycemia. Forty-six animals were used in the experiment but a statistical analysis is not provided. It is reported that some of the animals developed a conditioned reflex response to the experimental surroundings associated with irradiation, which was capable of producing a hyperglycemia at later times.

Lebedinsky (38) discusses the work of Lyubimova on changes in carotid sinus bioelectrical response to altered pressure in the sinus. After exposure of rabbits to 1000 r this parameter shows prompt increased

reactivity, followed by a distinct decreased reactivity at about the 3rd day. Unstable reactivity or return to normal occur after the 5th day.

Autonomic phenomena associated with irradiation of the head have also been investigated. Yu. I. Arkusskiy (4) observed changes in the activity of the heart following radiation of the brain. Dogs and rabbits were irradiated with a Co^{60} source, using doses of 250–3500 r to the temporal regions. Electrocardiograms (ECG) showed disturbances of rhythm, ectopic foci, decreased voltages and T-wave inversions. No lower threshold for these phenomena is stated, though they are also noted to have been seen with patients receiving cerebral radiotherapy.

V. A. Fanardzhyan *et al.* (13) report alterations in ECG activity following 5,000–10,000 r of gamma rays to the human cerebrum; the circumstances for this study are not given. A threshold of 5000 r is reported for divided doses. The findings include lowering of voltage peaks and slowing of contraction with unusual waves. Similar results were observed in the rabbit, with a threshold at 1000 r.

E. A. Fel'dman (15) observed a general rise in body temperature of 0.6–0.8 degrees centigrade in patients undergoing therapeutic irradiation of the head (15 per cent of an erythema dose was used). This effect is thought to be due to reactions on the part of cerebral vegetative centers. M. I. Nemenov (55) placed 43–80 millicurie radon preparations near the hindbrain of a decorticated cat and observed an increase in frequency and deepening of respiration within 15–30 minutes; the animals died in a state of hyperventilation.

P. G. Gurevich (24) conducted some experiments on white cell count alterations following irradiation of the rabbit cerebrum with doses of 600–900 r, using a field size of 2 x 2 cm. A significant drop in lymphocyte count was observed in 15 minutes, with a maximum by 24 hours (22 per cent), and recovery in 6–7 days. During control experiments in which the brain stem was radiated but the subcortical vegetative centers were shielded no or much smaller hematological changes appeared. Gurevich postulates that the action may be mediated by adrenaline released as the result of radiation.

The role of nerves from the spleen in the restitution of normal white count in acute radiation sickness has been investigated by T. K. Dzharak'yan (11). Experiments were done on rabbits given 700–900 r and cats given 350 r. Procedures included preliminary excision of the spleen, denervation one month before radiation and novocaine blockade before irradiation. The author concludes that all the experiments indicate a more rapid and complete recovery of white count when nerve connections to the spleen are *severed.*

Lebedinsky (38) quotes work by Gorizontov devoted to disturbances of thermoregulation in animals subjected to general irradiation, as demonstrated by the introduction of pyrogenic agents or diathermy heating. He also refers to the work of Portugalov on pathological studies of autonomic structures such as the sympathetic ganglia; the latter are said to show early histological alterations after radiation.

Vascular phenomena associated with irradiation have received considerable attention in the Soviet Union. Possible carotid sinus reactivity alterations after irradiation have already been noted. Ye. I. Komarov (29) reported on changes of blood pressure in cats subjected to 1200 r of whole-body radiation. Their blood pressure dropped by 20 points during the first days following irradiation and they also had a decreased pressor response to mechanical stimulation of the bladder or intestine. In his Geneva paper Lebedinsky refers to work by Gorizontov which purports to show a hypotensive agent in the cerebral blood of irradiated dogs; the presence of histamine in

such blood was also observed by this researcher.

T. K. Dzharak'yan and G. F. Fakhrutdinov (12) report on changes in intestinal-vascular reflexes following whole-body irradiation. Experiments were carried out on two dogs with exteriorized loops of intestine. Stimulation methods included elevation of intra-luminal pressure, perfusion of the loop with cold water and injection of potassium chloride or nicotine solution into isolated intestinal vessels. These stimuli were studied for their effect on blood pressure, pulse rate, respiratory rate and amplitude; also on small vessel tone, as shown by an ear plethysmograph.

The two dogs were given 400 r of hard x-rays, which resulted in the eventual death of one animal. It was found that, compared to controls, there was an increased response to pressure stimulation of the gut, as judged by respiratory rate and amplitude, pulse rate, and vascular contraction in the ear. All the responses were also notably prolonged, to the point of spasm in some cases. There was little effect, however, on the reaction to perfusion of cold water. In controls nicotine and potassium chloride solution were found to produce a transitory increase in blood pressure and decrease in respiratory rate. After irradiation these response were somewhat augmented and prolonged. In all cases the alterations in visceral responses paralleled the course of the radiation syndrome, with a maximum effect at 9–18 days. There appeared to be no early, immediate change after irradiation. The authors do not feel they can be sure which portion of the CNS is involved in such altered responses but suspect it to be subcortical structures.

Permeability changes in capillaries were given considerable attention by early radiation researchers. Some old work by Lasarew (37), repeatedly quoted by the Russians, investigated vasomotor phenomena in the ear of the rabbit following irradiation with 1.5–5.0 erythema doses. Responses to caffein, chloral hydrate and epinephrine were found to be abnormal at 2 hours, 2 days, a week and several weeks after irradiation. He concluded that these vessels showed phasic alterations which corresponded with the stages of erythema observed clinically.

S. M. Balmukhanov (6) noted that roentgen irradiation of the rabbit ear with 220 r resulted in an increased permeability of the vessel walls to trypan blue. Animals subjected to irradiation while under urethane narcosis did not show an increase in permeability until the narcosis was stopped, at which time there was a marked rise in permeability.

A. I. Gorban' (20) studied the effects of roentgen irradiation of the temporal region of the rabbit, using doses of 800–1000 r. An increase in intra-ocular pressure and permeability of ocular vessels was observed. Retrobulbar injection of novocaine or administration of chloral hydrate through an ear vein after irradiation resulted in a fall of intraocular pressure. The author concluded that this phenomena represents a roentgen erythema occurring inside the eye.

P. N. Kiselev (28) has discussed the possible mechanism of permeability alterations resulting from irradiation. He feels that they may be the result of a cellular release of hyaluronidase by some hypothetical nervous mediator substance, though the effect is not produced by local administration of acetycholine, histamine or leucotoxin. Lebedinsky (38) discusses the same hypothesis, stressing the role of hyaluronic acid, and reports work indicating that cholinergic nerve fibers may be responsible for activation of hyaluronidase after irradiation. His Geneva article contains references to the microscopic effects of radiation on capillaries, other studies on permeability alterations in the skin due to irradiation, and bioelectrical studies of the skin after radiation. He also mentions studies on serum mucopolysaccharide levels in connection with radiation sickness.

For many years the concept of a nervous "trophic" function has been generally accepted in the USSR, as a logical outgrowth of Pavlovian "nervism," according to which every tissue in the organism is under more or less immediate control of the central nervous system.

A good example of work along these lines is the bilateral production of ulcers in the legs of rabbits following unilateral local leg irradiation with high doses (5000 r), as reported in 1956 by Livanov (41). Earlier, V. A. Muzheyev and Ye. I. Bakin (53) observed changes in the ventral muscle of the frog following large doses from 20–25 millicuries of radium placed over the dorsal thoracic spine of the frog for 2–3 days. It is claimed that such changes were absent in animals which had been denervated prior to irradiation.

O. S. Il'ina (26) has discussed the effect of radon irradiation on the pigmentation and blanching reactions of the frog. She feels that changes in adrenaline production by the adrenal gland and alterations in skin permeability resulting from CNS effects are involved. N. A. Zhoga (73) reports that cerebral irradiation in rabbits with doses from 300–1500 r, using hard x-rays with a 3 x 4 cm field, leads to an accelerated dissemination of implanted malignant tumors, resulting in larger metastases. This was believed to be the result of altered cerebral trophic control. The production of pneumonias after very heavy cervical irradiation in the rabbit was also thought to be a trophic response by I. P. Dolgachev (10).

E. F. Galkovskaya (16) studied the effects of roentgen irradiation of the spinal cord in the axolotl with regard to speed of peripheral nerve regeneration. After doses of 10,000–20,000 r nerve regeneration was decreased only by a rather small amount (full recovery occurring 15 days later than in controls). Lebedinsky (38) reports some older work on nerve growth in which irradiation stimulated the growth of long nerve fibers that ramified into the epidermis but later degenerated; similar effects are said to have been found in connective tissue.

Livshits (45) summarizes the Soviet view on autonomic phenomena associated with radiation as follows: "At the present time it is experimentally proven that hyperglycemia, roentgen erythema and hypotonia induced by radiation have a neurogenic mechanism. . . ." He also mentions changes in tissue permeability in this connection. Considering the many possibilities for studies on trophic changes resulting from irradiation of the CNS it is perhaps significant that Livanov's paper on ulcer production in the rabbit foot was the only clear-cut trophic reaction reported in the Soviet materials reviewed by the author.

THE EFFECTS OF IRRADIATION ON CONDITIONED REFLEX RESPONSES

Since CR (conditioned reflex) studies are the backbone of Soviet Pavlovian physiological research it is not surprising to find a large number of Russian papers devoted to radiation effects on various types of conditioned reflexes. Unfortunately, quite a few of the papers are hard to evaluate because of inadequate consideration of controls, dosimetry, statistical analysis, and general experimental design, as well as reporting of a limited amount of data on the experiment.

The pioneer in the CR-radiation type study was M. I. Nemenov, who worked under the personal guidance of I. P. Pavlov. In one of his initial works (54) a dog was given 1500 r of hard x-rays through the top of the skull. Subsequently it showed CR's of normal size but "positive induction after a negative stimulus was replaced by residual inhibition." After an additional 2200 r to the head there was observed a sharp decline in all positive CR's, but this was followed by an increase that lasted for 8 days; later on the CR's again declined. It was stated in this original work that doses under 1500

r did not produce significant disturbances of CR activity.

Later on, however, M. I. Nemenov and V. V. Yakovleva (57) claimed that it was possible to demonstrate a higher degree of cortical sensitivity to radiation by the use of more complex experimental tasks. They gave two dogs 1000 r total doses to the head. One animal had an established delayed CR to a bell stimulus. Early after radiation the CR proved to be stronger; there was improved differentiation and delayed inhibition. The second dog also showed an initial increase in a positive CR and better differentiation. In a later phase (time not stated) the CR activity declined and CNS activity in general appeared to be compromised. A second dose of 500 r to the temple produced a "worsening in motility of nervous processes." The same authors also reported (56) that 1500 r (through the top of the skull) led to a decline in positive CR's, which was sometimes brief in duration. The apparent improvement in activity with the smaller doses was attributed to a weakening of reactivity to miscellaneous stimuli which normally might distract the animals.

Nemenov and Yakovleva also carried out a provocative experiment, quoted by Livshits (45) and apparently never repeated, in which irradiation of the head with 1500 r and simultaneous stimulation with either strong or weak auditory stimuli (siren or metronome) led to far greater disturbances of CR activity than seen when the same radiation was given without the associated auditory stimulation. It was postulated that the nervous system was more susceptible to radiation damage when in an excited condition.

N. N. Livshits, the author of the review which has here been widely quoted, has himself carried out a variety of experiments on CR-radiation effects. In 1953 he reported (44) on the effects of chronic whole-body irradiation using a daily dose of 10 r, given over 6–7 hours, from a Co^{60} source, with two dogs as subjects. In one animal, after 240 r cumulative dose there is stated to have been a decline of CR activity. The second animal, on the other hand, showed an initial improvement and a later decline in CR activity after a total of 500 r. This is related by Livshits to the Pavlovian classification of the animals' CNS type—for instance, the dog with a "weak type" of nervous system showed a decreased CR and "circular types of disturbances of higher nervous activity."

Livshits also did an experiment on three dogs using single doses of 200–400 r repeated at intervals of 1–3 months. Total doses are not stated. Exposures not causing overt symptoms of radiation sickness resulted in a ".... subacute worsening of differentiation and a decline in CR's lasting one day on the 17–25 day after irradiation .... Roentgen doses causing mild, temporary symptoms produced a marked increase in reflexes without improvement of differentiation and in some cases, 'equilibrating phases' and negativism...After doses inducing severe radiation sickness and death of the animals, there was a sharp decline in CR's with 'equilibrating' and 'paradoxical' phases; food was refused during the course of the experiment." No mention is made of the general condition of the animals in this latter phase, nor are the cumulative doses associated with the above reactions detailed.

In still another experiment, Livshits evaluated the effects of daily whole-body doses of 25 r (6 days a week) on digestive CR's. After a total of 600 r the two dogs studied "demonstrated acute disturbances in the dynamics of digestive CR's, in the presence of normal digestive excitability and without external signs of radiation disease.... Conditioned reflexes showed an early and profound disturbance, while unconditioned reflexes were affected only at a later time. .... Thus, experiments carried out by the method of conditioned reflexes show that

the cortex is highly reactive to whole-body irradiations."

Livshits describes some other work in which the cerebellum was given divided doses totaling 4000–6000 r (field size not specified). After this he felt that dogs of the "weak Pavlovian type" showed a "normalization" of CR activity, while in the case of one dog with a "strong Pavlovian type" somewhat lesser doses resulted in a worsening of differentiation.

Some provocative claims on CR's involving radiation effects have been made in the Soviet literature. M. A. Movsesyan and A. P. Arzumanyan (52) studied the effects of repeated doses of 100 r (to a total of 600 r) administered to the region of the liver in rabbits. They found an early leucocytosis and alterations in white cell counts at 20 and 120 minutes after irradiation. These authors state that the same type of white cell shifts could be produced by placing an animal in the environment used for irradiation.

N. N. Livshits (44) also did some experiments of this type. In his study, four rats, two rabbits and four dogs were given doses of 25–100 r, repeated 7–32 times, to the whole body. It is claimed that a CR was established to the environmental fixation used during irradiation. Livshits mentions both leucocytosis and leucopenia as significant indicators, as well as reticulocyte shifts, without providing any detailed data or statistical corroboration. Nonetheless the findings are described as showing the significant role played by the CNS in the hematological reactions associated with radiation.

Some Soviet workers have investigated the effects of scalp irradiation for ringworm in children with regard to effects on CNS functions. Livshits notes that Nemenov found a decline in CR activity lasting for about one and one-half months in such children. S. A. Lifshits (39) observed that, among small children subjected to roentgen epiliation, 80 per cent showed an increased "motor chronaxie" and 50 per cent showed increased "sensory chronaxie" in the flexor digit profundus muscles. Yu. M. Olenov (59) studied the effects of roentgen irradiation of the heads of newborn mice (120 r) on their CR activity in adulthood. Details of irradiation are not given. Two out of four mice so treated showed marked disturbances of CR activity as adults.

F. P. Mayorov *et al.* (49) investigated roentgen irradiations of the cervical sympathetic ganglia in the dog for possible influences on CR's. Doses ranged from 900–6000 r but no exact values are given in the original work. They found "reversible changes in CR's, analogous to those observed following ablation of the cervical ganglia."

We now turn to some of the latest available papers on the problem of the effects of radiation on conditioned reflexes. L. I. Kotlyarevskiy *et al.* (30) carried out experiments on white rats using successive doses of 50 r of x-rays. The response of the animals was studied by recording their movements when presented with visual or auditory stimuli previously associated with the placement of food behind a barrier, which the rat had to move in order to obtain the food. The first two doses of 50 r are stated to result in increased cortical excitability, followed by "active inhibition" and "phasic phenomena." Successive doses to a total of 150–350 r produced a decline of reflex activity, which occurred gradually, followed by a marked increase, which was also associated with phasic responses. The authors also note differing reactions in dogs of various Pavlovian CNS types, with the animals possessing a strong CNS type showing earlier recovery from higher doses. This article was analyzed by the reviewer and its conclusions are not supported statistically by the presented data; also the possibility of local gastric or non-nervous systemic reactions to radiation was not considered.

I. N. Piontkovskiy *et al.* (62) has reported on alterations in autonomic reflexes after radiation. Using a dose of 600 r Co–60 gamma rays in the white rat he finds an effect on motor digestive conditioned reflexes that lasts up to 10 months, especially after local irradiation of the abdominal region. Rabbits given 1500–5200 r show alterations in unconditioned respiratory and cardio-vascular reflexes.

Z. A. Yanson (71) studied the effects of 500 r on the CR of the rabbit. He reports that as early as 15–20 minutes after whole-body irradiation there is a failure of some conditioned protective reflexes. Some recovery occurs in a week but excessive inhibitory activity is present for 10–15 days and reflexes may remain unstable for an even longer time. Irradiation of the head alone with this dose causes the same effect, but with a more rapid recovery. After irradiation of the trunk alone CR activity remains approximately normal, but cortical function is thought to be affected, *e.g.*, a combination of conditioned and unconditioned stimuli leads to a prolonged abnormal inhibition.

In 1953 P. I. Lomonos (46) investigated gastric and whole-body irradiation, with shielding of the head, using doses of 750–4000 r, and noted acute effects on digestive CR's, while motor-protective reflexes revealed only equivocal changes. He concluded that these results were due to "an increase in the excitability of the subcortical protective center, which, as the result of negative induction, induced a decrease in digestive CR's." O. P. Bryukhanov and P. I. Lomonos (7) also reported on similar studies following intravenous injection of P^{32}. Doses of the isotope used are not stated and variable results are reported.

In a recent compendium on radiobiology (48) Lomonos reports on other work done with dogs; salivary reflexes reinforced by food or weak acid were investigated. After 700 r whole-body irradiation, he describes an increase in salivary CR's at 2–4 days, with a subsequent decline to below normal. Statistical analysis of the presented data shows a lack of any certainty, however. In another experiment 1500 r was given to an animal whose head was shielded. The animal showed an increase of CR's on the second day which lasted for a week; they then fell slightly below normal. After this time the animal became impossible to study due to excessive excitability. Another animal was given 300 r with protection of the head. The data in this case is strongly suggestive of an increase in CR activity on the first day, lasting a week, and then declining to somewhat below normal. Unconditioned reflexes, which are presented as controls, show a modest increase in response to acid stimulation. Another dose of 1000 r to the whole body produced only an apparent slight rise in CR activity, without definite change in unconditioned responses. Some work was also done with local gastric irradiation, using 750 r. This resulted in a decrease in digestive CR's lasting a week, followed by a period of variable response.

In another recent (1957) report, Lomonos (47) describes the effects of intravenous Co^{60} administration on CR activity in the dog. With doses of 0.18 to 2.6 millicurie per kg there appeared to be little effect on general cortical functions, although positive digestive CR's showed an early increase and there was some variability in the intensity of internal inhibition. A stereotype of salivary responses remained unaltered. Lomonos states that this experiment demonstrates the greater somatic effects of Co^{60} as compared to its cortical actions.

In his discussion of these experiments the author summarizes as follows. "We may suppose that both local and whole-body irradiation does not directly influence the strength of the cortical excitatory and inhibitory processes.... One may hypothesize that whole-body irradiation with roentgen rays in the dog induces some sort of pathophysiological changes that influence the subcortical protective center... The ob-

served phenomena may be explained by the assumption that weak excitation arising in the 'protective center' of the CNS is irradiated and reaches the 'digestive center'."

CONCLUSIONS

Reviewing the proceding materials, the writer finds it extremely difficult to reach definite conclusions as to the threshold for radiation effects that has actually been experimentally established in the Soviet work. Quite frequently the reviewed papers do not contain sufficient detail for a complete evaluation of the technique or conclusions. One cannot help but note lack of agreement between Soviet authors themselves on items like the effects of novocaine on early radiation sickness, initial alterations in CR activity, etc.

In particular the following omissions are evident in some of the reports: 1) lack of statistical analysis of results; 2) inadequate discussion of instrumentation and dosimetry (particularly as to depth dose); 3) limited use of controls (for example, three study animals and two controls in a very complex experiment on conditioned reflexes); 4) little information on the general condition of animals after irradiation (changes in CR's are given without mention of whether the animal was in a general state of health or post-irradiation cachexia); 5) limited analysis of experimental data (a given small strip of an EEG record may be presented in support of a certain point without supporting data as to reproducibility, presence in all animals, etc.); 6) failure to report negative findings as such (the writer has noted practically no Soviet papers giving a negative result for an experiment on CNS-radiation effects).

On the other hand, the Soviets have certainly obtained a number of results which, if they are confirmed, would be of the greatest theoretical and practical interest. Among their major findings the reviewer would note the following: 1) Evidence that though relatively inert to radiation morphologically, the CNS may be quite functionally sensitive to this noxious agent. Such sensitivity might be based on small random biochemical or bioelectric changes in many neurons or synapses. For instance, this type of effect may have been demonstrated in the work where 0.1 r is claimed to alter the variability (though not mean duration) of the rabbit knee flexor reflex latent period. 2) Indications that the first response to radiation may be increased activity in some parts of the CNS, a phenomenon which is strongly suggested by many cited experiments. This would put radiation in the same category as most cytotoxic agents, which, as is well known, often exert a mild stimulating effect in lowest doses. It has also been demonstrated by radiobiologists in all parts of the world that enzyme activity may be increased initially after moderate radiation exposures. There appears little doubt that radiation is depressing to the CNS in some sufficiently large quantity. 3) The theory that some sort of increased afferent inflow into the CNS due to stimulation of receptors by radiation may produce some abnormal nervous and physiological responses. One wonders, however, whether widespread body stimulation from heat, slight pain, vibration and noise, etc., would have a similar effect. 4) The much-emphasized Soviet concept that since the CNS plays an important role in all pathophysiological mechanisms a specific CNS role should be looked for in radiation pathogenesis. For example, detailed attention might be given to CNS participation in regeneration of bone marrow depleted by radiation. Such studies need not exclude consideration of humoral mechanisms, but rather supplement the latter approach. 5) The possibility that CNS damage from chronic exposure to radiation may be an important component in occupational or other radiation exposure.

The thresholds for CNS-radiation effects quoted by the Soviets are, of course, considerably below those widely accepted by

radiobiologists at present. Russian researchers have cited 10 r or even 0.1 r as causing significant changes in the rabbit knee flexor reflex. Forty roentgens is said to alter food-seeking activity. Livshits and others suggest that 200–400 r alters conditioned reflex responses. In regard to conditioned reflexes, however, it is of some interest that there is little unanimity among Soviet physiologists as to whether radiation increases or decreases CR responses, or how it influences latent periods, active inhibition, differentiation, extinction, etc.

The work on bioelectric phenomena reviewed in this paper seems to indicate a threshold at a few hundred r in mammals. The nature of EEG changes is hard to deduce, since they may be due to alterations in brain function or afferent activity, or other still more complex reactions. It is perhaps surprising that distinctive alterations have not been observed as yet at lower radiation doses. One should also note that from the experimental viewpoint, even at the above moderately high levels, it is essential to rule out the possible effects of extraneous stimuli, such as the sound of the x-ray machine going on.

In the last year or two there has been some noticeable change in the theoretical approach of many Soviet papers dealing with CNS effects of radiation. This reviewer concludes that the doctrine of Pavlovian "nervism" is being applied in more circumspect and less formal manner. Work on CNS effects of radiation and especially the CNS role in pathophysiology of radiation sickness continues on a large scale.

While the conclusions in certain of the reviewed Soviet papers may appear equivocal, it would seem most unwise to dismiss any of them until further research work is done. Quite probably recent Soviet work has demonstrated that the CNS is substantially more radiosensitive than has been widely assumed in the past. This makes it all the more important that similar research be undertaken by interested scientists in all parts of the world.

SUMMARY

1. Brief reviews are presented of a number of untranslated Russian research papers on the CNS effects of radiation.

2. In the USSR the CNS is considered as highly sensitive to radiation. Nervous system effects are said to have been demonstrated at as low as 0.1 r; many papers discuss effects with doses of a few hundred r. However, from the papers reviewed it does not seem possible to reach a final conclusion on CNS radiosensitivity.

3. A general critical analysis of the reported Soviet experiments suggests that there is some need for increased use of statistical analysis and controls, reporting of negative experiments, more complete documentation of findings, etc.

4. Possible important theoretical implications of the reviewed work are considered. They include the role of numerous random, neuronal disturbances on function; the effects of possible altered afferent activity due to stimulation of nerve fibers or receptors by radiation; alterations in nervous control of physiological activities such as bone marrow regeneration, etc.

5. It is presently thought in the Soviet Union that CNS irradiation effects may be important from the viewpoint of occupational radiation exposure and chronic exposure in general.

6. The role of the nervous system in radiation pathogenesis continues to be studied very intensively in the USSR. The major doctrines of Pavlovian "nervism" are now being applied in a somewhat less formal and apparently more circumspect way.

7. It is concluded that confirmation of a number of the cited experiments is urgently needed in order to fully document the lower limit of CNS radiosensitivity, both in chronic and acute exposure circumstances.

The opinions expressed in this review are those of the author and do not necessarily represent the viewpoints of the Division of Radiological Health of the U.S. Public Health Service, under whose sponsorship much of the work was done. This is particularly the case since the vast majority of originals are presently untranslated.

REFERENCES[3]

1. Aleksandrovskaya, M. M. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 58–61. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 60, 1957.
2. Antipenko, Y. I. et al. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 52–55. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 58, 1957.
3. Antipenko, Y. I. Quoted by Shikhodryrov., V. V. Sov. J. Atomic Energy, **2,** (2): 220, 1957.
4. Arkusskiy, Y. I. *All-Union Conf. Roentgenologists and Radiologists; Dissertations, June 16–20, 1952*, p. 14. Moscow, 1952. Quoted by Livshits (45).
5. Bakin, Y. I. Vestn. Rentgenol. i Radiol., (26): 67, 1946.
6. Balmukhanov, S. M. *Tr. Tsentr. In-ta Rentgenol. i Radiol. im. V. M. Molotov, 30th Anniversary Session, Dissertations. Moscow, 1954.* Quoted by Livshits (45).
7. Bryukhanov, O. P. and Lomonos, P. I. *Tr. Tsentr. In-ta Rentgenol. i Radiol. im. V. M. Molotov, 30th Anniversary Session, Dissertations. Moscow, 1954.* Quoted by Livshits (45).
8. Delitsina, N. S. *Proc. All-Union Conf. on Med. Radiol., 1957*, p. 65. Abstracted in Med. Ref. Zhurn., Ser. 4, **3:** 1958.
9. Dimitrov. L. A. Meditsinskaya Radiologiya, **2,** (4): 11–18, 1957.
10. Dolgachev, I. P. *All-Union Conf. of Roentgenologists and Radiologists, Dissertations, June 16–20, 1952*, p. 14. Moscow, 1952. Quoted by Livshits (45).
11. Dzharak'yan, T. K. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 49–51. Abstracted in Med. Ref. Zhurn., Ser. 4, 12: 59, 1957.
12. Dzharak'yan, T. K. and Fakhrutdino, G. F. Meditsinskaya Radiologiya, **3,** (2): 11–19, 1958.
13. Fanardzhyan, V. A. et al. Vestn. Rentgenol. i. Radiol., (4): 55, 1954.
14. Fedoreva, I. V. Meditsinskaya Radiologiya, **3,** (2): 32–37, 1958.
15. Fel'dman, E. A. Vrachnebnoe Delo, (10–11): 651, 1939.
16. Galkovskaya, E. F. D. A. N. U.S.S.R., **87:** 865, 1952.
17. Gamelaya, A. N. et al. Meditsinskaya Radiologiya, **1,** (5): 84–91, 1956.
18. Geynisman, Y. I. and Zhirmunskaya, Y. A. Fiziol. Zhurn. U.S.S.R., **38,** (3): 312, 1952.
19. Geynisman, Y. I. and Zhirmunskaya, Y. A. Vestn. Rentgenol. i. Radiol., (2): 5, 1953.
20. Gorban', A. I. Vestn. Rentgenol. i. Radiol., (3): 30, 1954.
21. Gorizontov, P. D. and Moroz, B. B. Vestn. Akad. Nauk. U.S.S.R., (3): 63, 1956.
22. Gorodetskiy, A. A. *Tr. Tsentr. In-ta Rentgenol. i Radiol. im. V. M. Molotov, 30th Anniversary Session, Dissertations.* Moscow, 1954. Quoted by Livshits (45).
23. Grigor'yev, Y. G. Vestn. Rentgenol. i. Radiol., (5): 3–10, 1954.
24. Gurevich, P. G. Vestn. Rentgenol. i Radiol., **20:** 51, 1938.
25. Gvozdikova, Z. M. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 34–39. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 58, 1957.
26. Il'ina, O. S. In *Problems of Radiobiology*, Pobedinskiy, M. N. and Kiselev, P. N., eds., pp. 36–43. Moscow, 1956.
27. Kekcheyev, K. K., Shayevich, Z. Z. and Anisimova, A. P. Byull. Eksp. Biol. i Med., **7:** 391, 1939. Quoted by Livshits (45).
28. Kiselev, P. N. *Biological Effects of Ionizing Radiations, Dosimetry, and Application of Radioactive Substances from the Therapeutic Viewpoint*, p. 3. Moscow, 1954. Quoted by Livshits (45).
29. Komarov, Y. I. Meditisinskaya Radiologiya, 2, (3): 3–7, 1957.
30. Kotlyarevskiy, L. I. et al. Meditsinskaya Radiologiya, **1,** (1): 11–19, 1956.
31. Kozlova, A. V. Vestn. Rentgenol. i Radiol., (4): 38, 1954.
32. Kruglov, A. N. and Klavdiyenko, I. M. Sovestk. Zdravookhr., Kirgizii, (3): 31, 1952. Quoted by Livshits (45).
33. Kudritiskiy, Y. K. Meditsinskaya Radiologiya. **2,** (3): 8–13, 1957.
34. Kudritiskiy, Y. K. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 55–58. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 58, 1957.
35. Kuznetsov, V. I. et al. Voen-Med. Zhurnal, **2:** 40–43, 1957. Abstracted in Med. Ref. Zhurn., **3:** 62, 1958.
36. Lapitskiy, D. *Tr. In-ta po Izych. Mosga im V. M. Bekhtereva*, p. 113. Moscow-Leningrad, 1935. Quoted by Livshits (45).
37. Lasarew, N. W. *Strahlentherapie.* 1926–27. Quoted by Livshits (45).
38. Lebedinsky, A. V. The influence of ionizing radiation on animal organisms. Peaceful Uses of Atomic Energy, **11:** 7–24, 1956.
39. Lifshits, S. A. *The Chronazimetric Study of the Effects of Roentgen Rays on the Central Nervous System.* Thesis. Leningrad, 1947. Quoted by Livshits (45).
40. Livanov, M. N. Meditsinskaya Radiologiya, **1,** (1): 19–27, 1956.
41. Livanov, M. N. Klin. Med., (3): 12, 1956.

[3] Since volume number is not indicated in all Russian journals, issue number is frequently cited and uniformly enclosed in parentheses in this listing.

52. Livanov, M. N. and Kaburneyeva, L. I. Meditsinskaya Radiologiya, **3**, (1): 9–16, 1958.
53. Livanov, M. N. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 17–22. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 53, 1957.
54. Livshits, N. N. *Inst. of Biochem. Acad. of Sciences, Ukrainian S. S. R., Conf. on Biochem. of the Nervous System, December 15–19, 1953*, p. 36. Kiev, 1953. Quoted by Livshits (45).
55. Livshits, N. N. The nervous system and ionizing radiation. In *Ocherki po Radiobiologii* (Notes on Radiobiology), pp. 151–233. Moscow, 1956.
56. Lomonos, P. I. Vestn. Rentgenol. i Radiol., (4): 30, 1953.
57. Lomonos, P. I. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 44–49. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 59, 1957.
58. Lomonos, P. I. In *Problems of Radiobiology*, Pobedinskiy, M. N. and Kiselev, P. N., eds., pp. 5–20, Moscow, 1956.
59. Mayorov, F. P. et al. *Jubilee Session, Dedicated to the 100 Birthday of I. P. Pavlov, Dissertations*, p. 75. Moscow-Leningrad, 1949.
60. Mikhaylovskiy, B. G. *Tr. Tsentr. In-ta Rentgenol. i Radiol. im V. M. Molotov, 30th Anniversary Session, Dissertations*. Moscow, 1954. Quoted by Livshits (45).
61. Movsesyan, M. A. et al. *Inter-Republic Conf. of Soviet Oncologists and Roentgenologists, Azerbijan, Armenian and Georgian S. S. R.*, p. 46. Tiflis, 1951. Quoted by Livshits (45).
62. Movsesyan, M. A. and Arzumanyan, A. P. Izv. AN Armyanskoy S. S. R., (5): 53, 1952. Quoted by Livshits (45).
63. Muzheyev, V. A. and Bakin, Y. I. Byull. Eksp. Biol. i Med., **7**, (2–3): 146, 1939. Quoted by Livshits (45).
64. Nemenov, M. I. Vestn. Rentgenol. i Radiol. **11**, (1): 1932. Quoted by Livshits (45).
65. Nemenov, M. I. and Mozharova, Y. N. Vestn. Rentgenol. i Radiol., **20:** 8, 1938.
66. Nemenov, M. I. and Yakovleva, V. V. Vestn. Rentgenol. i Radiol., **22:** 1, 1940.
67. Nemenov, M. I. and Yakovleva, V. V. Vestn. Rentgenol. i. Radiol., **26:** 43, 1944.
68. Nikitin, S. A. and Maksimchuk, Y. P. Tr. Odessk. Rentgenol. In-ta, **1:** 69, 1933. Quoted by Livshits (45).
69. Olenov, Y. M. Vest. Venerol. i Dermatol., (4), 1950. Quoted by Livshits (45).
70. Olenov, Y. M. and Pushnitsyna, A. D. D. A. N. U.S.S.R., **84:** 405, 1952.
71. Oleynikova, T. N. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 61–65. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 60, 1957.
72. Piontkovskiy, I. N. et al. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 39–43. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 59, 1957.
73. Poplavskiy, N. K. Meditsinskaya Radiologiya, **1**, (5): 10–13, 1956.
74. Semenov, L. F. *Changes in Tissue Nucleoproteids Associated with the Action of Roentgen Rays on the Organism*. Thesis. Leningrad, 1951. Quoted by Livshits (45).
75. Semenov, L. F. and Prokudina, B. A. Meditsinskaya Radiologiya, **2**, (3): 35–40, 1957.
76. Shapiro, Y. Y. Arkh. Patol. Anat. i Patol. Fiziol., **7:** 30, 1941. Quoted by Livshits (45).
77. Shefer, D. G. *Roentgen Rays and the Central Nervous System*. Rostov, 1936. Quoted by Livshits (45).
78. Sizenko, S. P. and Markevich, V. V. Meditsinskaya Radiologiya, **3**, (2): 72–78, 1958.
79. Ugodskaya, L. N. and Yudin, Y. G. Meditsinskaya Radiologiya, **3**, (4): 11–18, 1957.
80. Ul'yanova, A. I. and Shmelev, V. P. Meditsinskaya Radiologiya, **3**, (2): 19–23, 1958.
81. Yanson, Z. A. *Proc. All-Union Conf. on Med. Radiol., 1957*, pp. 23–28. Abstracted in Med. Ref. Zhurn., Ser. 4, **12:** 57, 1957.
82. Zhdanov, I. M. *Tr. Tsentr. In-ta Rentgenol. i Radiol. im V. M. Molotov*, **5:** 159, 1941. Quoted by Livshits (45).
83. Zhoga, N. A. Vrachebnoe Delo, (6): 438, 1953.

THE RELATIONSHIP OF THE BLOOD BRAIN BARRIER OF THE RAT TO I^{131}-LABELLED TRIIODOTHYRONINE[1]

DONALD H. FORD, PH.D.[2]

The ability of the central nervous system (CNS) to take up I^{131}-labelled triiodothyronine (T_3) has been demonstrated in several species (3–5, 11). While the actual concentration is rarely high, the CNS may achieve levels of total radioactivity which are twice those of the plasma (4). The ability of the CNS to take up T_3 becomes more apparent when the total radioactivity of the CNS and plasma is fractionated chromatographically and the concentrations of T_3, alone, are compared, since the CNS T_3-level increased with time while the plasma T_3-level decreased (3–5). That this radioactivity was due primarily to extravascular radioactive compounds, has been shown in the rabbit and rat in which injections with Radio Iodinated Serum Albumen (RISA) demonstrated that the activity associated with the blood trapped in the vascular spaces was too low to account for the radioactivity found in the brain. Indeed, the amount of radioactivity associated with the vascular space was too low to even necessitate a correction factor when one calculated the per cent of the injected dose taken up by the CNS (3, 5).

While there is little doubt but that the CNS is capable of concentrating thyroid hormones, the actual per cent of the injected dose taken up remains quite small, being less than 0.1 per cent of the injected dose in the rabbit and rat in most instances, and only slightly higher in the guinea pig (3–5). This suggests that the so-called Blood Brain Barrier (BBB) considerably slows the entry of T_3 into the CNS. The following experiments were designed to answer three questions concerning the relative effectiveness of the BBB in slowing the uptake of T_3 by the CNS.

1. *Can triiodothyronine enter the CNS more readily if injected via the subarachnoid space or fourth ventricle?* The possibility that this might occur was suggested by experiments (7) which showed that progesterone appeared capable of penetrating the ependymal ventricular lining in the hamster to induce psychic estrus in estrogen-primed spayed females. Of further interest in this regard are the autoradiographic studies of Koenig (8) who has observed incorporation of adenine-8-C^{14}, orotic-6-C^{14} acid, L-methionine-S^{35}, and glycine 2-H^3 into the intracellular nerve protein following intracisternal or subarachnoid injection in the cat or rabbit. The incorporation of amino acids into neural protein when injected into the cisterna magna has also been observed by Gaitonde and Richter (6), using S^{35}-labelled methionine in the rat. These observations indicate that, although protein complexes of the injected amino acid or nucleic acid precursors may have been formed with the small quantities of albumen and globulin found in the cerebrospinal fluid (CSF), enough of the injected amino acid or nucleic acid precursors membranes to become incorporated into protein of the nerve cell elements. Thus, it does not seem improbable that T_3 might also be able to enter the CNS by this route.

2. *At what rate does T_3 enter tissues such as the skeletal muscle which one does not usually think of as possessing a vascular-tissue barrier comparable to the Blood Brain Barrier, and how does this rate and*

[1] This study was supported by Grant No. A-1530 from the National Institutes of Health of the Public Health Service.

[2] Department of Anatomy, State University of New York, College of Medicine, Brooklyn, New York. The author wishes to acknowledge with thanks the technical assistance of Mrs. Marie Buschke and Mr. Ralph Rhines.

total uptake compare with those observed in the CNS? This should indicate to what extent the BBB may or may not inhibit CNS uptake of triiodothyronine as compared with other tissues.

3. A third problem related to the concentration of thyroid hormone by the CNS is essentially the reverse of question #1, and pertains to the possibility that *if T_3 can pass through the ependyma into the CNS, it may also pass from the CNS into the CSF.* In a previous communication it was noted that there was some iodide in the CSF of the rabbit following injecting of labelled-T_3. Inasmuch as the identification of the CSF iodide, in this instance, was based on a small sample having a very low specific activity, it seemed possible that small traces of T_3 and other metabolites might have been overlooked or lost in the chromatographic procedure. In view of this possibility, a reinvestigation of the problem seemed appropriate.

MATERIALS AND METHODS

The methods for these experiments may be conveniently divided into two major categories; a) those concerned with the effectiveness of the Blood Brain Barrier, and b) those dealing with the passage of T_3 from the CNS into the CSF.

The I^{131}-labelled T_3 was obtained in a 50 per cent propylene glycol solution from the Oak Ridge Laboratories of the Abbott Corporation. The various procedures for dilution, testing of purity (66–85 per cent T_3), preparation of standards, methods of counting and chromatographic analysis and autoradiography, have been previously discussed (2–5). Suitable saline dilutions were prepared for injection into the animals.

One phase of the study concerned with determining the relative effectiveness of the BBB for T_3 was to examine the possibility that T_3 might more readily enter the CNS if it were injected into the subarachnoid or brain ventricular spaces, thus bypassing the BBB. For these experiments three male guinea pigs weighing from 600 to 800 grams, and one male rat weighing 350 grams were used, each animal receiving a dose of 0.5 μg. of T_3/kg. (approximately 15.2 μc./kg.; the actual microcurie dosage varied according to the specific activity of the material used). One guinea pig was injected intravenously. The neck muscles were dissected away to expose the dura between the base of the skull and the first cervical vertebra in the remaining two guinea pigs and in the rat. One guinea pig was injected into the fourth ventricle, while the injections into the other guinea pig and the rat were into the cisterna magna. The volume of injection into the cisterna magna or fourth ventricle was 0.05 ml. following withdrawal of an equivalent volume of CSF. The animals were killed one hour after receiving the labelled hormone; the brains and pituitaries were quickly removed and fixed in 10 per cent neutral formalin. The brains were then subdivided (3) and counted in a scintillation counter. The per cent of the dose taken up and organ/plasma ratios were determined from the counts of radioactivity present. The brains from the intraventricular or cisternally injected animals were then prepared for autoradiography. Since the counts from all parts of the CNS but the medulla, pons and cerebellum of the cisternally injected guinea pig and rat were not above background, only autoradiographic data from these animals will be presented.

Three additional guinea pigs were included in the autoradiographic study to obtain autographs for comparison with those prepared from the animals receiving the cisternal or ventricular injection. One received a dose of 1 mc. of Na I^{131}, one a dose of 1 mc. of I^{131}-labelled T_3/kg., and the third an equivalent volume of physiological saline. All were injected intravenously and sacrificed two hours later by cardiac perfusion with citrated physiological saline while under anesthesia. The autoradiographs from the Na I and saline injected animals were negative, while the

animal receiving the labelled hormone showed the nuclear concentrations previously indicated (4) and is representative of five similarly treated animals.

The second phase of the investigation as to the relative effect of the BBB on the entry of T_3 into the CNS was to compare the concentration of CNS-T_3 at varying time intervals with the concentration in other tissues where such a barrier is lacking. For this purpose 15 normal rats were utilized, using five different time intervals; at a dose level of 0.5 μg./T_3/kg. (approximately 15.2 μc./kg.). The rectus abdominis muscle, kidney, liver and adrenal were taken for comparison with the CNS and pituitary. The tissues were then counted in a scintillation counter.

In the series of experiments dealing with the possible transmission of T_3 into the CSF (from either the choroid plexus or the CNS), several species of animals were used. Included were two male, one diestrous and two pregnant female guinea pigs weighing from 600 to 800 gm.; two white male rabbits weighing 2.4 and 2.9 kg.; two mongrel male dogs weighing 5.5 and 5.7 kg.; one ovariectomized cat weighing 2.0 kg. and one male rhesus monkey weighing 3.85 kg. All animals except the monkey received an intravenous injection of I^{131}-labelled T_3 and were killed at varying times after receiving the injection. The monkey received a perivenous injection into the soft tissue surrounding the internal jugular vein and is included in this series only because some radioactivity was found in the CSF, despite what were considered to be very low CNS and CSF values. A chromatographic analysis of the CSF was done on only the rabbits, since they were not only large enough to provide large CSF samples, but small enough to ensure a high concentration of labelled hormone in the plasma and CNS. Attempts to chromatograph CSF samples from the guinea pig were unsuccessful due to very small volumes which were obtainable.

The dosage of T_3 used for the guinea pigs, dogs and the monkey was 0.5 μg./kg. (approximately 15.2 μc./kg.). The cat received a dose of 1.02 μg./kg. (30.5 μc./kg.) while the two rabbits received 7.25 and 11.3 μg./kg. (414 and 550 μc./kg.) respectively.

In one animal which received a fairly large dose of T_3 (19.8 μg./kg.; 200 μc./kg.) having a purity of 60.5 per cent, a sample of peritoneal fluid was taken, counted and chromatogrammed to provide data pertaining to the ability of T_3 to pass through other tissue membranes than the ependymal linings of the ventricle or pial-glial membrane limiting the outer surfaces of the CNS.

RESULTS

Experiments on uptake of T_3 from the cerebrospinal fluid: The data listed in Table 1 suggest a significant increase in the concentration of radioactivity in the guinea pig CNS when the I^{131}-labelled T_3 was administered into the fourth ventricle. It is also apparent that a very small per cent of the injected material reached the blood after ventricular injection, since there was radioactivity in the terminal plasma. Inasmuch as the autoradiographs (to be discussed later) showed some radioactivity in the subarachnoid spaces after ventricular injection, it seems likely that the radioactivity in the plasma may have reached the plasma vascular compartment by passing through the arachnoid granulations after escaping from the fourth ventricle. On further inspection of Table 1, it becomes apparent that there is a lack of uniformity in the concentrations of radioactivity of even adjacent parts of the CNS. While the very low per cent of the dose in the cerebral grey may be due to lack of penetration through the white matter, the variations between adjacent areas of the brain stem (*i.e.*, tuberal and chiasmic diencephalon; cerebellum, pons and medulla) suggest that the radioactive hormone may have only been

adsorbed onto the ventricular surface of the various structures.

Autoradiographic study confirmed the suggestion that the increased concentration of radioactivity in the CNS was due primarily to the adherence of the radioactive material onto the ventricular walls (A, B, C, D, E and F, Figure 1), after intraventricular injection. In no instance was there evidence of nuclear localizations similar to those seen after intravenous injection (AA, BB, CC, DD, EE, FF, Figure 1). At the injection site in the medulla (A-1), some diffusion through the brain parenchyma was observed where the ependymal lining was broken by the needle during injection. The rather wide band of exposure seen where the film was adjacent to the ventricular wall suggests that there has been some penetration of the radioactive material across the ependymal lining. However, the application of the injected material into the rather restricted ventricular system has provided what might be termed a focal accumulation of radioactivity with a sufficiently high gamma ray emission to produce much scatter on the film, particularly on the very sensitive No-Screen X-ray film used for these autoradiographs. Therefore, the wide band of reaction observed to be on either side of the ependymal lining of the ventricles, being equally positive over cell-free regions, appears to be primarily due to scatter. However, while it is concluded that the apparent radioactivity (indicated by autoradiography), deep to the ependymal lining of the diencephalon, was due to such scatter, some may still have been due to a slight penetration of the labelled hormone or of free iodide.

The region of the subarachnoid spaces in the medulla (A), pons (B), cerebellum (C), and midbrain (D) was autoradiographically positive, indicating that some of the injected material had either escaped through the foramena of Luschka into the subarachnoid space or been injected into the cisterna magna, as well as the IVth ventricle. In regions where the arachnoid and pial membranes were damaged during processing (Figure 1, C-10, D-10), there was much less radioactivity, confirming the association of the peripheral rim of radioactivity in the sections with the subarachnoid space. There was no evidence of penetration into the brain parenchyma from this space. Autoradiographs were not made of the cerebral grey, since it was considerably mutilated when it was separated from the underlying white matter.

The dorsolateral aspect of the diencephalon (Figure 1, E and F) was also observed to be autoradiographically positive. Since this surface was not directly in contact with either a ventricular or subarachnoid space, it has been concluded that some activity escaped from the ventricular region during fixation and embedding, and subsequently adhered to this surface. This band is much less distinct than that observed in the sub-

TABLE 1

The Per Cent of the Dose of I^{131} Present in the Guinea Pig CNS 60 Minutes After Intravenous or Fourth Ventricular Injection of I^{131}-Labeled Triiodothyronine (0.5 μg./kg.)

Injection Site	% Dose/Gram		Organ/Plasma Ratio	
	Intravenous	IVth Ventricle	Intravenous	IVth Ventricle
Terminal plasma	0.15	0.008	—	—
Adenohypophysis	0.82	0.030	5.50	4.30
Neurohypophysis	0.42	0.070	2.79	8.90
Medulla	0.14	4.78	0.91	560.00
Pons	0.14	1.84	0.97	210.00
Cerebellum	0.14	2.02	0.96	235.00
Midbrain	0.14	1.66	0.91	194.00
Isol. Mammil. Body	0.13	2.95	0.86	385.00
Tuber. Dienceph.	0.11	1.36	0.72	156.00
Chiasm. Dienceph.	0.09	4.28	0.62	490.00
Cerebrum	0.12	—	0.82	—
Cerebral Grey	—	0.15	—	19.00
Cerebral White	—	3.60	—	415.00
Caudate Nucleus	—	14.40	—	1660.00
Choroid Plexus Lateral Ventric.	—	77.00	—	8900.00
Choroid Plexus IVth Ventricle	—	43.00	—	4950.00

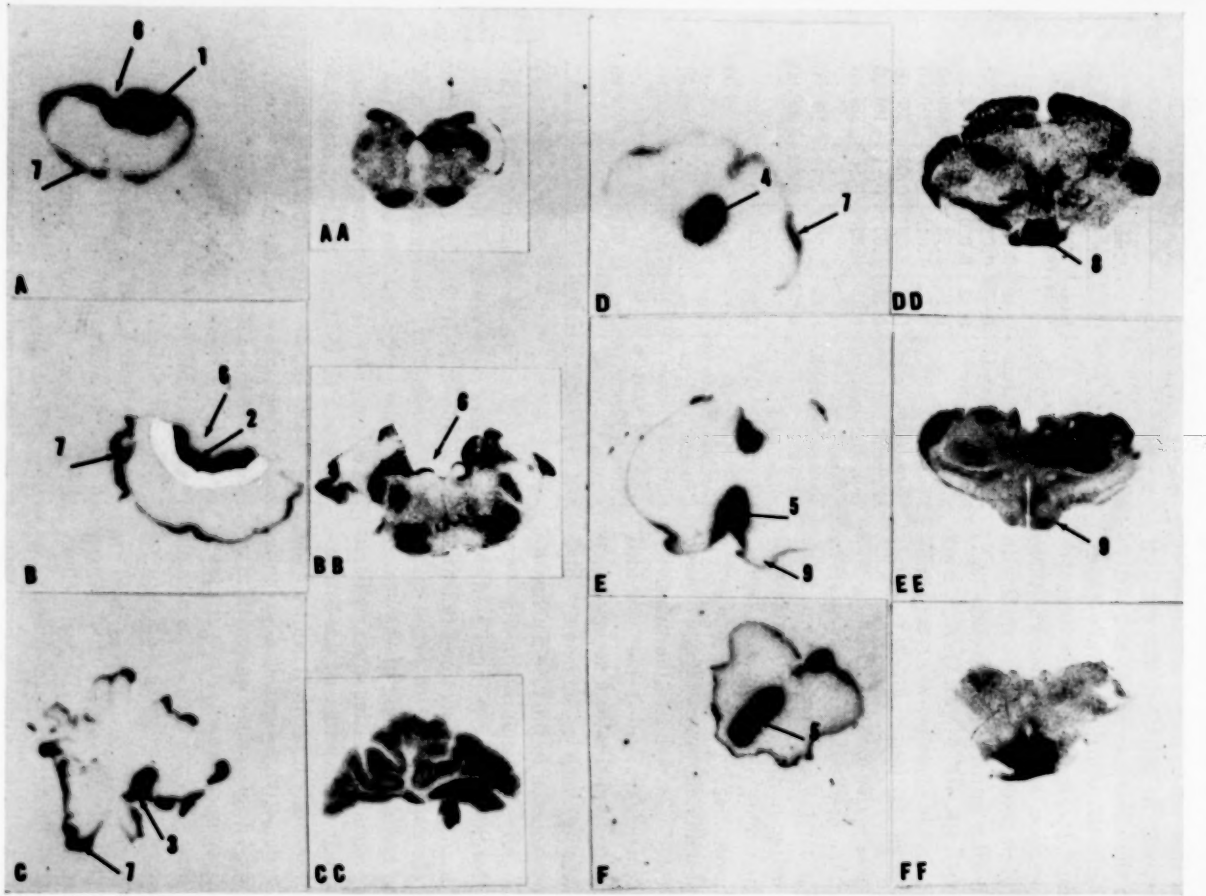


FIG. 1. The autoradiographic localization of radioactivity in the brain of the male guinea pig after intraventricular injection (indicated by single letters) or after intravenous injection (indicated by double letters) of I^{131}-labelled triiodothyronine. The dotted line indicates the ependymal surface. A and AA = open medulla; B and BB = pons; C and CC = cerebellum; D and DD = midbrain (superior colliculus); E and EE = tuberal diencephalon; F and FF = chiasmic diencephalon. 1. Injection site into the IVth ventricle and underlying medullary parenchyma; 2. Radioactivity adhering to ependymal lining of IVth ventricle in pons; 3. Fastigial recess; 4. Region of the subcommissural organ at point where the aqueduct of Sylvius joins the IIIrd ventricle; 5. IIIrd ventricle; 6. IVth ventricle; 7. Subarachnoid space; 8. Mammillary body; 9. Median eminence; 10. Areas where pial-arach-

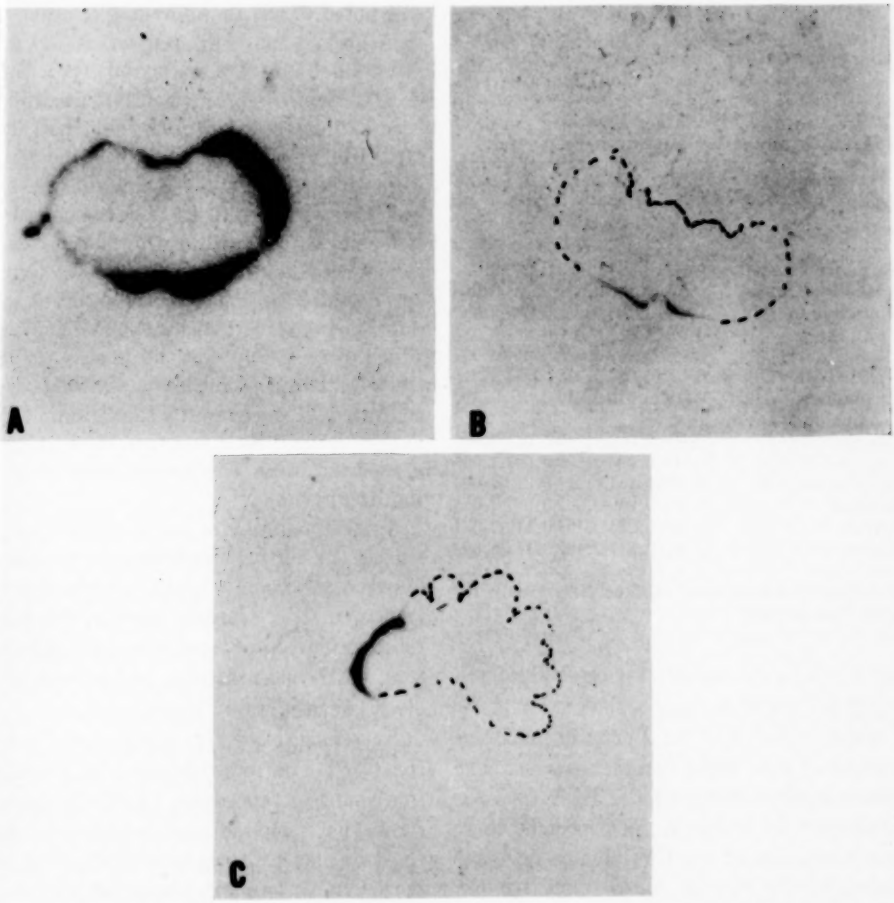


FIG. 2. The autoradiographic localization of radioactivity in the male guinea pig after an intracisternal injection of I^{131}-labelled triiodothyronine. The dotted lines were added to indicate the outline of the rest of the section, where the radioactive hormone failed to fill any part of the subarachnoid space. A = open medulla; B= pons; C = cerebellum.

arachnoid spaces, particularly in E (Figure 1), whereas that part of the diencephalon adjacent to a ventricular cavity or subarachnoid space is much more clearly responsive. This band is actually more distinct in these photographic reproductions than it was in the autoradiograph.

The autoradiographs in Figure 2, obtained following intracisternal injection, are very faint probably because of the loss of the injected material through the injection-site. Apparently, the volume which remained was insufficient to circulate further rostral than the ponto-cerebellar region, since there was no radioactivity associated with the midbrain or cerebrum. A small amount may have entered into the fourth ventricle, but did not migrate up the cerebral aqueduct. As in the previous animal injected in the fourth ventricle, no or very little radioactive material penetrated the CNS. Similar results were observed in the male rat with the radioactivity being restricted to the subarachnoid space around

TABLE 2

Concentration of I^{131} in the Plasma, Central Nervous System, Pituitary, Muscle, Adrenal, Liver and Kidney of Fifteen Normal Male Rats after I.V. Injection of 0.5 μg./kg. of I^{131}-Labelled Triiodothyronine. The Figures are Expressed in μg. of Triiodothyronine/100 gm. of Tissue

Tissue	Time in Hours Since Injection				
	0.5	1.0	2.0	4.0	7.0*
Terminal Plasma	0.062	0.047	0.043	0.036	0.024
Adenohypophysis	0.126	0.133	0.137	0.107	0.049
Neurohypophysis	0.089	0.108	0.052	0.042	0.027
Brain Stem	0.012	0.011	0.013	0.014	0.011
Cerebellum	0.013	0.012	0.013	0.014	0.009
Isolated Mam. Body	0.013	0.022	0.018	0.021	0.018
Remainder Diencephalon	0.011	0.010	0.012	0.016	0.012
Cerebral Grey	0.008	0.009	0.010	0.011	0.006
Cerebral White	0.005	0.005	0.006	0.007	0.005
Skeletal Muscle	0.046	0.011	0.014	0.013	0.009
Adrenal	0.155	0.090	0.062	0.037	0.053
Liver	0.351	0.274	0.133	0.119	0.034
Kidney	0.445	0.317	0.162	0.114	0.060

* Three animals were used to obtain data for each time period.

the medulla, caudal inferior cerebellum and basal surface of the diencephalon.

Experiments on CNS T_3 concentration as compared with those in other tissues: The relative effectiveness of the BBB to T_3 is illustrated in Table 2. As expected, there was much less of the I^{131}-labelled hormone concentrated by the CNS than by the adenohypophysis (identification of the radioactive material previously determined (3–5)). Liver and kidney, and to a lesser extent the adrenal, were also clearly able to concentrate T_3 more rapidly. These tissues showed a rapid early concentration and then a rather rapid fall in concentration while the CNS showed a slower uptake during the first hour which was then well maintained during the rest of the experiment. Studies with RISA (3, 5) have shown that this radioactivity in the CNS exceeds considerably the concentrations which might be attributed to the radioactivity of blood trapped in the neural tissues. When the CNS concentration of T_3 is compared with that of the skeletal muscle, however, less difference was noted. True, the muscle, like other tissues, had an initial concentration (30 min. after injection) approximately 3.5 times greater than the brainstem, but this difference had disappeared in the next half hour after which brain and muscle concentration were strikingly similar. Only the cerebral grey and white failed to achieve concentrations similar to those of the muscle. Thus, the skeletal muscle, which has a vascular space similar to that observed in brain (unpublished observations by Dr. Fedinec) and which presumably has no real vascular-tissue barrier comparable to the BBB, concentrated T_3 more rapidly than did the CNS in the first half hour, but then showed levels of concentration similar to those seen in the brainstem.

Autoradiography of peripheral guinea pig tissues (2) further illustrates the similarity between CNS and skeletal muscle concentration of T_3. Cardiac muscle, by autoradiographic procedures, was slightly higher than CNS concentrations, and smooth muscle was considerably lower.

Experiments on the transfer of T_3 into the CSF: The data obtained by scintillation counting procedures (Table 3) demonstrate that some radioactive material enters the CSF, since traces of activity were observed in all animals, regardless of sex. In the male guinea pig, pregnant female guinea pig and in the male rabbit, the per cent of the injected dose of I^{131} taken up increased slightly with time. Although there was some variation in the per cent of the dose concentrated in animals killed after the same interval following injection (dog), the impression obtained from most of the data was that there was a slight increase with time. If one may include the half-hour diestrous female guinea pig (such an animal would be expected to be under minimal female hormonal influence) with the quarter- and one-hour male guinea pigs, the impression of an increase in concentration of radioactivity in the CSF with time is even stronger.

TABLE 3

A Comparison of the Per Cent Dose of I^{131} in the Cerebrospinal Fluid, Central Nervous System and Plasma at Various Time Intervals after Intravenous Injection of I^{131}-Labelled Triiodothyronine in the Guinea Pig, Rabbit, Cat, Dog and Rhesus Monkey

	Animal	Duration Exp. in Hrs.	Dose μg./kg.	% Dose in CSF	% Dose in CNS	% Dose in Plasma	CNS/CSF Ratio	Plasma/CSF Ratio
1	Male Guinea Pig	¼	0.50 μg.	0.0050	0.119	0.290	23.8	55.50
2	Male Guinea Pig	1	0.50 μg.	0.0130	0.107	0.131	8.2	10.00
3	Female Guinea Pig Diestrous	½	0.50 μg.	0.0103	0.075	0.152	7.4	14.80
4	Female Guinea Pig Pregnant	½	0.50 μg.	0.0030	0.109	0.150	35.1	50.00
5	Female Guinea Pig Pregnant	1	0.50 μg.	0.0050	0.146	0.160	29.3	32.50
6	Male Rabbit	2	7.25 μg.	0.0007	0.026	1.050	36.0	85.00
7	Male Rabbit	4	11.30 μg.	0.0011	0.035	0.045	35.0	41.00
8	Ovariectomized Cat	2	1.02 μg.	0.0068	0.016	0.048	2.3	7.05
9	Male Dog	2	0.50 μg.	0.0001	0.002	0.010	22.0	88.00
10	Male Dog	2	0.50 μg.	0.0003	0.005	0.026	18.0	92.50
11	Male Rhesus* Monkey	3	0.50 μg.	0.0003	0.006	0.022	18.3	72.00

* Perivenous Injection.

Even the rhesus monkey, whose dose of T_3 was inadvertently injected in the soft tissues surrounding the internal jugular vein, demonstrated an uptake of I^{131} into the CSF. The route whereby the injected material reached the CSF in the monkey can not be clearly ascertained. However, it may have entered into the lymphatic plexi located in the region of the injection site and then very quickly entered into the venous system through the lymphatic ducts. From the venous blood, the T_3 could presumably reach the CNS without difficulty. The probability of the injected material following such a path seems reasonable since the concentrations reached in the CSF, CNS, and plasma were as high as those seen in the dog after intravenous injection.

That the amount of I^{131} in the CSF was very low is emphasized when its concentration is compared with that observed in the CNS and plasma (Table 3), and it may also be observed that the CNS levels of radioactivity are from 7.4 to 36.0 times greater than those of the CSF. Plasma concentrations were still greater, being from 10.0 to 92.5 times higher than CSF values.

The nature of the radioactive material present in the CSF was determined by ascending paper chromatography (Table 4), using a butanol-dioxone-ammonia solvent system. The greatest per cent of the radioactive material present in the CSF of the rabbit was observed to be T_3, with lesser values being noted for free iodide and the unidentifiable compounds lumped together as residue. The per cent of the radioactivity attributable to T_3 was also observed to have increased between the 2nd and 4th hours after injection. Similar increases in T_3 concentration with time have been observed in the CNS (Table 1, (5)). In this, the CSF

TABLE 4

Metabolites of I^{131}-Labeled Triiodothyronine in the Plasma, Cerebrospinal Fluid and Central Nervous System of the Rabbit 2 and 4 Hours After the Injection of 1 mc. of Labelled Hormone

	Plasma		Cerebrospinal Fluid		Central Nervous System	
	2 Hour	4 Hour	2 Hour	4 Hour	2 Hour	4 Hour*
	%	%	%	%	%	%
Triiodothyronine	64.4	57.7	40.7	50.8	77.9	90–96
Iodide	18.7	23.3	30.4	33.3	2.7	4–10
Residue	16.9	19.0	28.9	15.9	19.3	—

* Estimated from the density of an autoradiogram of a chromatographic analysis of the brain from the animal.

TABLE 5

A Comparison of the Per Cent of the Dose and Organ-Plasma Ratio of I^{131} in Rat Brain, Liver, Kidney, Muscle, Plasma and Peritoneal Fluid Two Hours after an Injection of I^{131}-Labelled Triiodothyronine

Dose of Triiodothyronine	19.8 μg./kg.	(A)*	0.5 μg./kg.	(B)†
Tissue	% dose	organ/plasma ratio	% dose	organ/plasma ratio
Plasma	0.423	—	0.316	—
Medulla	0.162	0.383	0.120	0.417
Cerebellum	0.163	0.385	0.131	0.486
Mammillary Body	0.223	0.525	0.192	0.663
Cerebral Grey	0.129	0.305	0.103	0.347
Liver	1.135	2.682	—	—
Kidney	1.998	4.722	—	—
Striated Muscle	0.212	0.501	0.125	0.449
Peritoneal Fluid	2.757	7.050	—	—

Per Cent of Metabolites of Triiodothyronine present in Peritoneal Fluid

Triiodothyronine	Iodide	Mono & Diiodotyrosine	Residue
27.58	64.25	0.84	7.32

* One experimental animal with a high dose of triiodothyronine (19.8 μg./kg.).

† Seven normal animals which received only a tracer dose of labelled hormone (0.5 μg./kg.).

was unlike the plasma, where the radioactivity attributable to T_3 fell with time, as did the total plasma radioactivity (3, 5).

If triiodothyronine is capable of passing from brain parenchyma with its sub-microscopic extracellular spaces (9, 10) through the ependymal cellular membrane, is it possible that it may also pass through other thin cellular membranes into body cavities? The peritoneal lining of the abdominal cavity, which is permeable to the body fluids, is such a membrane.

In one large rat which received 19.8 μg/kg. (200 μg/kg.), a large sample of colorless peritoneal fluid was taken and its concentration of radioactivity compared with that from brain and plasma (Table 5-A). The figures in section B (Table 5) represent the mean values from seven normal rats which received a dose of 0.5 μg. of T_3/kg. and are included only to show that the dose of T_3 given to the animal listed in Column A, which was 39.5 times greater than that which is usually given in tracer studies, does not proportionately increase the per cent of uptake of I^{131}. Indeed, two of the seven normals had per cent dose uptake values larger than those seen in the animal with the 19.8 μg./kg. dose. One may conclude, therefore, that the high dose given to the animal in A would not be expected to appreciably alter the per cent of the dose found in the various organs. As previously indicated, the striated muscle does not appear to differ greatly from the CNS in its ability to concentrate T_3 after the first thirty minutes. The peritoneal fluid contained a very high per cent of I^{131} as compared with other tissues, the total radioactivity/gm. being exceeded only by the thyroid which picked up 15.6 per cent of the injected dose/gm. While much of the radioactivity identified in the peritoneal fluid by paper chromatography was iodide, a significant proportion was T_3 (27.58 per cent). Since the purity of the material injected was only 65 per cent T_3, the peritoneal fluid T_3 level dropped 57 per cent. It is to be noted that the available level of T_3 in the plasma usually drops 49.5 per cent in an equivalent period (5), therefore, the level of T_3 in the peritoneal fluid seems to have closely paralleled that which would have been seen in the plasma. From these data there appears to be little or no barrier to the flow of I^{131} containing metabolites of injected I^{131}-labelled T_3 across the peritoneal lining membranes of the abdominal cavity.

DISCUSSION

Briefly, there are several points to be noted from this series of studies. First, T_3, unlike methionine (6), adenine, orotic acid or glycine (8), does not enter the CNS to any extent when it is injected into the cerebrospinal fluid spaces of the ventricles or subarachnoid space. When T_3 was injected into these spaces, it seemed mainly to adhere to the ependymal membrane or the

pialarachnoid membranes without penetration.

Indeed, why should the caudate nucleus, some considerable distance from the medulla, have a higher concentration than at the medullary injection site, or why should the choroid plexus of the lateral ventricles be more radioactive than that of the fourth ventricle, unless these counts represent only an indiscriminate adsorption of the labelled T_3 at various sites without regard to actual penetration of the ependymal linings? Some variations in concentration at opposite ends of the neuraxis might have been expected due to withdrawal of some of the injected material as it ascended through the ventricular system. However, the wide variations and high concentrations in the caudate nucleus and choroid plexus of the lateral ventricle do not fit into a concept of gradual withdrawal of the injected material into the various parts of the brain stem as it ascends through the cerebral aqueduct, qualitatively less being available for absorption in the diencephalic-telencephalic regions than in the ponto-medullary areas.

Conceivably, this amino acid hormone may have become bound to larger protein molecules which might have prevented its entry. While this may be true to some degree, chromatographic analysis of CSF from animals injected via the intravenous route (Table 4) contained an appreciable amount of free iodide and T_3 not associated or bound to any protein. Therefore, it seems probable that the T_3 injected into the CSF spaces would not be prevented from entering the CNS because of some binding with protein. Thus, the ependyma and pial-glial coverings of the CNS actually seem to represent more of a barrier to the entry of free T_3 into the CNS than does the BBB.

The relative degree of efficiency of the BBB to T_3 was further studied by comparing CNS concentrations of radioactivity with those observed in other tissues (Table 2). While there is little doubt but that T_3 enters the liver, kidney, adrenal and hypophyseal tissues faster than it does into the CNS, the difference between brain and skeletal muscle was not as remarkable. That brain and muscle may be favorably compared in regard to uptake of T_3 is further indicated by the fact both tissues have about the same vascular space, since the observed blood space of rat CNS (organ/plasma ratio of from 0.0049 to 0.0078; (5)) is in the same range as that observed in rat muscle (Fedinec, unpublished data). Indeed, once an early muscle uptake period has passed (30 minutes), brain and muscle concentrations are remarkably similar. However, the fact that muscle shows a prominent early peak, like the liver, suggests a fairly unrestricted uptake, followed or accompanied by a rapid utilization which reduces the amount of I^{131} to levels comparable to brain levels, very quickly. Inasmuch as the uptake of T_3 into the brain after the first 30 minutes so closely parallels that of the muscle, one might conclude that the BBB represents only a slightly more serious impediment to the entry of T_3 into the CNS of the rat than does the cellular or tissue membranes separating skeletal muscle tissue from the blood. Certainly the muscle does not seem able to concentrate the injected material more rapidly than the CNS after the initial high plasma levels of labelled material have dropped, unless it is metabolizing it so rapidly that the labelled hormone fails to accumulate when the blood levels are so low. This is certainly possible.

In the second phase of the experiments it was pointed out that some radioactivity may be detected in the CSF of the guinea pig (male or female) rabbit, cat, dog or rhesus monkey. This was true whether the I^{131}-labelled T_3 was given intravenously or into the perivenous tissues (monkey). The per cent of the injected I^{131} present in the CSF was also observed to increase slightly with time, paralleling what was observed in the CNS (4, 5). As indicated before, the plasma levels of total radioactivity decrease with time (3–5).

Chromatographic studies of rabbit CSF

showed that a considerable per cent of the CSF radioactivity was due to T_3 and that this per cent increased with time, as did the per cent due to iodide, while the unidentified compounds in the residue decreased. The radioactive compounds in the CSF are, therefore, more like those in the CNS than those in the plasma in the changes which occurred with time.

Since the CSF concentrations of I^{131} are very low in every instance, even when compared with CNS values, it would appear that some barrier must exist between the CSF and the blood stream and CNS for T_3 and its metabolites. This barrier might be contained within either the choroid plexus or the ependymal lining of the ventricular system, or both. While the plasma level of total radioactivity was higher than that of the CNS, it seemed unlikely that this higher plasma concentration of I^{131} could account for the CSF-T_3 concentration, even though one might have expected the plasma to be the origin of the CSF radioactivity on the basis of it having a higher T_3-pressure gradient than would be present in going from the CNS to the CSF. That the CSF-T_3 level cannot be based with confidence on a concept of such pressure-gradients was suggested by the observation that that per cents of the various T_3 metabolites found in the CSF paralleled those of the CNS rather than those of the plasma. As CNS-T_3 increased, so did that of the CSF; as residue decreased, so did that of the CSF, while the reverse condition was observed in the plasma. Furthermore, both CNS and CSF concentrations of total radioactivity increased with time, while those of the plasma decreased. Indeed, the observations on the percentages of metabolites present and the temporal changes of total radioactivity which occurred suggest that the CSF-T_3 concentration is more closely related to that of the CNS. Therefore, the conclusion has been tentatively reached that the slight traces of radioactive material observed in the CSF represent substances which have first entered into the CNS and have then passed through the ependymal lining of the ventricles into the CSF. Some radioactivity may also reach the CSF by passing through the pial-glial membranes into the Virchow-Robbin spaces from which it could pass out into the CSF in the subarachnoid space.

While the principal pathway for movement of T_3 may be from CNS to CSF, the data does not preclude the possibility that some I^{131}-labelled compounds may reach the CSF by passing through the choroidal membranes. Possibly the T_3 and its larger metabolites pass through the ependymal lining from the CNS while some free iodide may pass through the choroid plexuses. The likelihood that such an active metabolic compound can cross membranes lining body spaces, such as from brain into CSF via the ependyma, appears to be substantiated by the observation that T_3 can also pass across the peritoneal membranes into the peritoneal space lining the abdominal cavity (Table 5).

Thus, triiodothyronine, a metabolically active compound, appears to enter the rat CNS from the vascular system almost as easily as it does into muscle, though at a slower rate than was observed for liver, kidney, adrenal or pituitary. Inasmuch as T_3 injected into the CSF spaces did not enter the CNS, a pathway for entry of T_3 into the CNS by diffusion through the choroid plexuses into the CSF and subsequent absorption through the ependyma into the brain parenchyma seems unlikely. (Such a pathway would be similar to the one postulated by Bakay for phosphate (1, p. 60)). The changing concentrations of CSF-T_3 metabolites, which paralleled those seen in the CNS rather than those observed in the plasma, would also seem to rule out such a pathway for entry of T_3 into the CNS since the changes in CSF radioactivity concentrations seem more to suggest a flow from CNS to CSF, rather than vice versa.

In conclusion, while some barrier in the

brain vascular bed may exist for T_3, it is probably only a slight one. Furthermore, such T_3 as enters the brain parenchyma appears able to diffuse into the CSF by passing through either the ependyma or pial-glial membranes. This CSF radioactivity can presumably then re-enter the vascular compartment through the arachnoid granulations. In such a system, the CSF can perhaps be likened to a brain lymphatic drainage system aiding, in this instance, in the removal of excess T_3 and its metabolites.

SUMMARY

The effectiveness of the Blood Brain Barrier in inhibiting the entry of I^{131}-labelled triiodothyronine (T_3) into the brain has been studied. The data indicate that there is relatively little barrier between the brain and vascular system for T_3, which was observed to be concentrated by neural tissues almost as effectively as by striated muscle. However, when the labelled T_3 was injected in such a manner as to circumvent this "barrier", it was found, by autoradiographic studies, that the ependymal and pial-glial membranes were relatively impermeable to triiodothyronine.

While T_3 could not pass from the cerebrospinal fluid into the brain parenchyma, it did appear to go in the reverse direction since detectable amounts of radioactivity were found in the cerebrospinal fluid of several species following intravenous injections of labelled hormone. The radioactive material in the cerebrospinal fluid of the rabbit was subsequently shown to contain considerable amounts of triiodothyronine. The most likely pathway for entry of T_3 into the cerebrospinal fluid seemed to be by diffusion through the ependyma or pial-glial membranes; thus suggesting a one-way transfer of T_3 across these membranes. Radioactive material was also observed to pass from vascular or tissue spaces across the peritoneal lining of the abdominal cavity into the peritoneal fluid. This, too, contained a large amount of triiodothyronine.

To conclude, the entry of T_3 into the brain of the rat does not seem to be markedly delayed in comparison with its entry into skeletal muscle when the hormone reaches the brain through its normal vascular channels. Some of the T_3, which enters the brain, reaches the cerebrospinal fluid, possibly by diffusion across the ependymal or pial-glial membranes. This shift from brain to cerebrospinal fluid appears unidirectional since I^{131}-labelled T_3 injected into the cerebrospinal fluid failed to penetrate these membranes.

REFERENCES

1. Bakay, L. *The Blood Brain Barrier.* C. C Thomas, Springfield, Ill., 1956.
2. Ford, D. H., Corey, K. R. and Gross, J. The localization of thyroid hormones in the organs and tissues of the guinea pig: An autoradiographic study. Endocrinology, **61:** 426–444, 1957.
3. Ford, D. H. and Gross, J. The metabolism of I^{131}-labelled thyroid hormones in the hypophysis and brain of the rabbit. Endocrinology, **62:** 416–436, 1958.
4. Ford, D. H. and Gross, J. The localization of I^{131}-labelled triiodothyronine and thyroxine in the pituitary and brain of the male guinea pig. Endocrinology, **62:** 549–560, 1958.
5. Ford, D. H., Kantounis, S. and Lawrence, R. The localization of I^{131}-labelled triiodothyronine in the pituitary and brain of normal and thyroidectomized male rats. Endocrinology, **64:** 977–991, 1959.
6. Gaitonde, M. K. and Richter, D. The metabolic activity of the proteins of the brain. Proc. Roy. Soc. London. s. B., **145:** 83–99, 1956.
7. Kent, G. C., Jr. and Lieberman, M. J. Induction of psychic estrus in the hamster with progesterone administration via the lateral brain ventricle. Endocrinology, **45:** 29–32, 1949.
8. Koenig, H. An autoradiographic study of nucleic acid and protein turnover in the mammalian neuraxis. J. Biophys. & Biochem. Cytol., **4:** 785–792, 1958.
9. Maynard, E. A., Schulz, R. L. and Pease, D. C. Electron microscopy of the vascular bed of rat cerebral cortex. Am. J. Anat., **100:** 409–433, 1957.
10. Schultz, R. L., Maynard, E. E. and Pease, D. C. Electron microscopy of neurons and neuroglia of cerebral cortex and corpus callosum. Am. J. Anat., **100:** 369–407, 1957.
11. Taurog, A., Harris, G. W., Tong, W. and Chaikoff, I. L. The uptake of I^{131}-labelled thyroxine and triiodothyronine by the neurohypophysis. Endocrinology, **59:** 34–47, 1956.

INTEGRATION AND DIFFERENTIATION IN SCHIZOPHRENIA

HAROLD F. SEARLES, M.D.[1]

From a purely descriptive viewpoint, schizophrenia can be seen to consist essentially in an impairment of both *integration* and *differentiation*—which are but opposite faces of a unitary growth-process. From a psychodynamic viewpoint as well, this malfunctioning of integration-and-differentiation seems basic to all the bewilderingly complex and varied manifestations of schizophrenia.

Taking first the matter of *integration*, we find that when we assess the schizophrenic individual in terms of the three classical structural areas of the personality —id, ego, and superego—we discover these to be poorly integrated with one another. The id is experienced by the ego as a Pandora's box, the contents of which will overwhelm one if it is opened. The ego is, as many writers have described, severely split, sometimes into innumerable islands which are not linked discernibly with one another. And the superego stands in the nature of a cruel tyrant whose assaults upon the weak and unintegrated ego are, if anything, even more destructive to it than are the accessions of the threatening id-impulses, as Szalita-Pemow (16), Hill (9) and others have emphasized. Moreover, the superego is, like the ego, even in itself not well-integrated; its utterances contain the most glaring of inconsistencies from one moment to the next. Jacobson (10, 11) has shown that there is actually a dissolution of the superego, as an integrated structure—a regressive transformation back into the threatening parental images whose conglomeration originally formed it.

Differentiation is a process which is essential to integration, and *vice versa*. For personality structure-functions or psychic contents to become integrated, they must first have emerged as partially differentiated or separated from one another; and differentiation in turn can emerge only out of a foundation of more-or-less integrated functions or contents.

When we look, now, at this process of differentiation in the schizophrenic person, we find it to be, similarly, severely impaired. It is difficult or impossible for him to differentiate between himself and the outer world. He often cannot distinguish between memories and present perceptions; memories experienced with hallucinatory vividness and immediacy are sensed as perceptions of present events, and perceptions of present events may be experienced as memories from the past. He may be unable to distinguish between emotions and somatic sensations; feelings from the emotional sphere often come through to him as somatic sensations, or even as variations in his somatic structure (changes in the size, color, and so forth, of bodily parts).

He cannot distinguish between thoughts and feelings on the one hand, and action on the other hand; thus if the therapist encourages him to explore thoughts and feelings of a sexual or murderous nature, for example, he feels that the therapist is trying to invite him into sexual activity, or incite him to murder. He may be unable to differentiate, perceptually, one person from another, so that he is prone to misidentifying them.

In the conduct of his daily life and in his communicating with other persons, he is unable, as Bateson *et al.* (3) have reported, to distinguish between the symbolic and the concrete. If his therapist uses symbolic language, he may experience this in literal

[1] Chestnut Lodge, Rockville, Maryland. This paper is an outgrowth of work, in the Chestnut Lodge Research Institute, which is being financed by a grant from the Ford Foundation.

terms; and on the other hand the affairs of daily life (eating, clothing himself, sleeping and so on) which we think of as literal and concrete, may be reacted to by him as possessing an unique symbolic significance which completely obscures their "practical" importance in his life as a human being.

I have stressed how interwoven are the growth processes of integration and differentiation, and it follows that the impairments of both are likewise interwoven. But in the schizophrenic these two processes tend to be out of step with one another, so that at one moment a patient's more urgent need may be for increased *integration*, whereas at another moment he may more urgently need increased *differentiation*. And there are some patients who show for months on the end a more urgent need in *one* of these areas, before the alternate growth-phase comes on the scene. Thus there is a modicum of validity in speaking here of two different "types" of schizophrenic patients. This is a largely artificial distinction, but useful for the purpose of exposition.

THE "NON-INTEGRATED TYPE" OF PATIENT

The predominantly "non-integrated type" of patient, then, can be further described as characteristically being several, or even many, different persons to the various nurses and aides on his ward. In extreme instances, he fosters marked dissension among them, as each responds to a different fragment of his poorly-integrated ego. Each personnel-member, regarding this fragment as being the patient's whole ego, feels sure that he or she knows the "real" Mr. Smith, and becomes violently at odds with fellow personnel-members who are equally convinced of the total validity of the other ego-fragments to which they are relating.

In his psychotherapeutic hours, he shows extreme changeability from one moment to the next. One woman, for example, suddenly pauses in the midst of vicious paranoid tirades at me, to ask me in a calm and friendly way for a light for her cigarette. Or he may relate to the therapist on two quite different levels of feeling simultaneously. For instance, a hebephrenic young woman, in trying to sit on one's lap, may be at once a lustful woman and a pathetic little child.

As to such a patient's subjective experience of this non-integration, we find above all that his experience, as regards both current living and memories of the past, is lacking in continuity. Because his ego is too weak to tolerate in awareness his intense, poorly-integrated or ambivalent feelings, these are largely dissociated or repressed, and projected onto the outer world which is therefore experienced as chaotically changing; thus an intolerable experience of chaotically-changing feelings within is averted. One such woman told me, seriously and convincingly, after I had repeatedly tried to learn something from her about her mother, "Whenever you use the word mother, I see a whole parade of women, each one representing a different point of view." This same woman, for approximately the first three years of our work, felt innumerable gaps in her own consciousness of current living; was sure that there were thousands of different Chestnut Lodges among which she was constantly shifted, all over the world; and was sure that there were several different Dr. Searleses, with one being replaced by another from one day to the next and even from one moment to the next. When her fragmentation was at its height, she was convinced even that her body was only a conglomeration of anatomical parts from various other persons; and other persons' bodies, including mine, were perceived similarly by her.

Two other women I have treated gave me to realize that, over the course of many months, my face was perceived by them as constantly changing, from something beautiful to something monstrous, and so on.

One hebephrenic man sat for months, in our hours, watching my face entirely as if he were watching a fascinating movie, grunting often in astonishment, pleasure, or awe, and on rare occasions verbalizing his experience of seeing, at the moment, a beautiful rose, a dilapidated Cape Cod house, a sex fiend, or whatnot.

One hebephrenic woman, after many months of evidencing anxiety and antagonism in response to my moving about, or changing posture, finally let me know that when, for example, on a warm day I got up and shifted my chair around to the opposite side of her bed, to be closer to the open window, she experienced it that there were now two of me in the room, much as if one were unable, in watching a motion picture, to see it as one continuous motion, but saw it as broken up into a series of "stills"; in this patient's instance, moreover, the "stills" remained on the scene, and accumulated. I now understood better why she had complained anxiously, in session after session earlier in her therapy, that there were 200 or 300 doctors in the room. She let me know also, on another occasion, that whenever I changed posture, she misidentified me as some different person from her past.

In turning now to the therapist's typical feeling-responses in sessions with such patients, let us acknowledge first the gratifications which he finds in an oftentimes dramatic experience of finding the wide gamut of his feeling-capacities played upon, in fascinatingly unpredictable ways, over the course of the therapeutic session, in response to the amazingly varied part-persons, so to speak, of which the unintegrated patient is comprised.

But all too frequently any such gratification is erased by the anxiety and helplessness, the threat to his own personal integration and his own sense of identity, which he feels upon experiencing suddenly changing, intense emotional responses to the poorly-integrated patient, or upon finding himself feeling, even, on two different levels simultaneously toward the patient—levels of powerful affect without any felt connection between these levels. Thus he may find his feelings unpredictably switching, in response to the patient's deeply fragmented modes of expression, from intense fury at one moment to deeply-moved compassion the next moment, and back again. Or he may feel simultaneously aroused sexually in response to the patient's seductiveness, and utterly incongruously maternal toward the infantile needfulness which she is at the same time evidencing in another area of her behavior.

Further, such a patient tends naturally, and healthily, to identify wholeheartedly with the therapist, as a refuge from the fragmentation which overwhelms him—as a means of finding, in symbiotic relatedness to the mother-therapist, a sufficient island of wholeness so that he can now turn, to phrase it in an oversimplified way, and integrate the dissociated components of his personality, one by one, until such time as he has sufficient ego of his own to endure the resolution of this symbiosis. Benedek (4–7), Mahler (13), and Michael Balint (1, 2) have pointed out that a symbiotic relatedness, which many earlier writers had described as *per se* pathological, is actually necessary to normal infancy. My experience indicates, further, that such a relatedness constitutes a necessary phase in psychoanalysis or psychotherapy with either neurotic or psychotic patients, respectively, and that this phase is especially important in the therapy of schizophrenic patients, for in their histories even that very early life-stage was severely distorted.

Such a symbiotic relatedness involves not only intense gratifications for the therapist, but intense anxiety also; on occasion his sense of identity may be severely threatened by his felt oneness with a deeply fragmented schizophrenic person. I cannot overemphasize, however, the importance of the therapist's being as open as possible

to the whole gamut of feeling-responses which such a deeply-fragmented patient tends to arouse in him. This is essential to the development of the "therapeutic symbiosis" which I have just described; by contrast, a patient cannot deeply identify with —become subjectively at one with—a therapist whose own feelings are kept largely under repression. Further, one of the major functions of this symbiosis is, in my experience, that it enables the patient's increasing integration to occur as it were *external* to himself, in the intrapsychic experience of the therapist, as a prelude to its development at an intrapsychic level within the patient himself. Mystical though this sounds, it is based upon logically understandable clinical phenomena.

In one case, for instance, I repeatedly reacted to a schizophrenic woman as being a combination of murderous woman and appealingly needful child. Toward the murderous woman in her I felt fear and anger; toward the child, I felt friendliness, tenderness, and compassion. Moreover, in varying degrees I inevitably *expressed* such feelings, both verbally and non-verbally, to each of these two so-called persons in her. This phase in the evolution of my view of her, this kind of feeling-responses on my part toward her, was a necessary prelude to the development which finally came next, after many months; namely, I suddenly realized, in the course of one hour with her, that she was a single person whose personality contained both these so different aspects.

Such a feeling-realization, such a felt "knowing," is not easy to come by; more than once I have heard therapists, in staff presentations, describe their relationship with a schizophrenic patient in such a manner as to make clear that they are not really describing a person, but a conglomeration of symptoms or personality-fragments. But once the relationship has progressed sufficiently far—once, to phrase it another way, the patient's integration has proceeded sufficiently far—that the therapist can achieve such an integrated inner picture of the patient, from now on he inevitably responds to the patient in this vein, namely, as *a person*, and in accordance with long-known theories of the development of the self, the patient, in finding himself persistently so responded to by the therapist (and, increasingly from now on, by others in his environment), comes in course of time to the feeling-realization that he is a person, comes to such an image of himself at an unconscious as well as a conscious level.

My technical suggestions concerning one's work with this "type" of patient relate to what has just been said concerning the growth process involved in the therapeutic relatedness. A patient cannot identify with a therapist who is running off in all directions after the patient's various personality fragments; instead, the therapist will find that, very frequently, the most useful move is to "stay put" psychologically, simply acknowledging the feeling or feelings which the patient is endeavoring to convey. Such responses from the therapist, when well timed, foster the gradual building up of consensually-validated accretions to the patient's conscious ego.

Equally important is the therapist's keeping in as close touch as possible with the location of what one might call the patient's conscious ego, where his sense of identity resides. If the therapist responds to a personality-fragment which is dissociated—that is to say, one of which the patient is unaware—the patient is likely to feel entirely out of touch with him, and grossly misidentified by him. When one has had, oneself, the experience of being repeatedly, or even constantly, misidentified by a patient in session after session—being responded to as myriad persons other than oneself, one knows how intense is the anxiety aroused by this experience of feeling misidentified.

And when a patient is expressing two affects simultaneously, it is important that the therapist acknowledge both, if both

seem to be in the patient's awareness, or to acknowledge more emphatically that of which the patient is more fully aware. Suppose, for example, a patient is consciously and verbally demanding to be allowed to leave the hospital, and simultaneously in non-verbal ways is revealing a dissociated desire to be kept in the hospital. If, now, the therapist responds only by saying, "That's all right; I know you *really* want to stay here. Rest assured that I realize this," one can see how maddening this is to the patient, how likely it is to increase his anxiety and his feeling of helplessness. If one says instead, "I know that you're determined to leave, and that you feel you can't stand it here another day; but I wonder if such-and-such behavior suggests, too, that something in you feels very differently about it?" this is, in my experience, at least less likely to be traumatic. And most frequently, I find it wisest to make *no* comment about the such-and-such behavior unless I see some indication that the patient is at least partially aware of it himself.

The final technical point I wish to make, with regard to the non-integrated "type" of patient, concerns the usefulness of transference-interpretations. We see that in the work with such a patient, transference-interpretations may have a specifically therapeutic effect, for they may help to focus into the therapeutic relationship itself the patient's multiple ego-fragments which are tending to fly off in all directions and remain attached to innumerable disparate persons outside the therapeutic relationship. Transference - interpretations may facilitate, that is, the patient's becoming whole *via* his recognizing all these diverse experiences of his as consisting, in part, in reactions to the therapeutic relationship, and specifically to the wholeness of the therapist's personality. But here a note of caution is needed, for, as Lidz and Lidz (12) have pointed out, premature or overly-abundant interpretations of this sort tend to make the patient feel—correctly, I believe (15)—that the therapist is trying to incorporate him, as did one or another of his parents in earlier years. And I have seen that he may react with an increase in his personality-fragmentation, as an unconscious defense against the incorporatively-oriented therapist's transference interpretations.

THE "NON-DIFFERENTIATED TYPE" OF PATIENT

This patient, in marked contrast to the one just discussed, has a relatively static, unvarying relatedness with the various personnel-members on the ward; he has a relatively fixed social role which changes but little over months or even years. Rather than the personnel's being, as with the former type of patient, in a state of marked dissension as to who this person is, their views of him coincide all too closely. And with this stereotyped social role on the ward, he fosters also a markedly stereotyped relationship with the therapist, such that the therapist as well feels him to be a relatively little-differentiated personality. In his therapeutic sessions he is often mute and motionless, and such verbalizations or physical movements as he exhibits are stereotyped, relatively unvarying month after month.

The patient's subjective experience of his poorly differentiated state is, of course, difficult for us to know, for in most such instances he is mute, or nearly so. One such man told me, in a rare moment of verbal communication, that his thoughts would often flicker down, like a candle flame, and be extinguished; another phrased it that it was as though a giant hand were squeezing down his inner experience, more and more constrictingly. A number of such patients have let me know that their perhaps most usual experience was of being alone in a dead, empty world; one man phrased it

that he was "in a mist." Most of the time, from what I have seen, they feel themselves to be dead.

Insofar as they are aware of the world around them, they see this world in global or homogeneous terms, with little if any differentiation. The therapist, for instance, if he emerges at all into their awareness as something distinct from his background, is perceived as but one head in a many-headed mass which includes all other persons in the surroundings, as if he were but one of the many heads in the Hydra of Greek mythology. And the patient's family members are not perceived as a group of differentiated individuals, but as "The Family," entirely comparable with "The Hospital" of which the therapist is perceived as but an indistinguishable part. In many instances, so far as I have been able to determine, the patient feels himself to be a similarly indistinguishable part of The Family or of The Hospital.

One patient felt herself to be conterminous with the bed in which she lay, and perceived me as being a part of the chair in which I sat next to her bed, very similar to the perceptions which Savage (14) and others have described as typical of subjects with LSD-induced psychoses. One of my patients said, "I'm wrapped up in this building," and when she first began coming to my office, she let me know that she was filled with a sense of anxious apartness from her self, this self being thoroughly bound up with the hospital room in which she had long been housed.

One comes to realize, in working with such a patient, how premature have been one's efforts to find out what feelings the patient is experiencing or what thoughts he is having; one comes to realize that much of the time, he has neither feelings nor thoughts, differentiated as such and communicable to us.

Such differentiation as the patient possesses tends to crumble when intense emotion enters his awareness. A paranoid man, for example, may find that when his hatred toward another person reaches a certain degree of intensity, he is flooded with anxiety because he no longer knows whether he hates, or instead "really loves" the other individual. This is not based, I believe, primarily upon the mechanism which Freud (8) outlined in his classical description of the nature of paranoid delusions of persecution, a description in which repressed homosexual love played the central role. The central difficulty is rather that the ego is too poorly differentiated to maintain its structure in the face of such powerful affects, and the patient becomes flooded with what can only be described as *undifferentiated passion*, precisely as one finds an infant to be overwhelmed at times with affect which the observer can not specifically identify as any one kind of emotion.

As for the feelings which the therapist himself experiences in working with this second "type" of patient, we find, here again, a persistent threat to the therapist's sense of identity. But whereas in the first instance the threat was felt predominantly as a disturbance of one's personal integration, here it is felt predominantly as a weakening of one's sense of differentiation. In this instance, the "therapeutic symbiosis" which I mentioned before is also, in my experience at least, a necessary development, and I believe that it tends to occur earlier here, for this patient's predominant mode of relatedness with other persons, at the developmental level at which we find him at the very beginning of our work, is a symbiotic one. I have already described how the symbiotic relatedness, with its subjective absence of ego-boundaries, involves not only special gratifications but anxiety-provoking disturbances of one's sense of personal identity.

The comparatively rapid development of symbiotic relatedness is facilitated by the patient's characteristically non-verbal, and

physically more or less immobile, functioning during the therapeutic sessions. In response, the therapist's own behavior becomes more and more similar, so that each participant is now offering to the other, hour after hour, a silent, impassive screen which facilitiates abundant mutual projecting and introjecting. Thus a symbiotic state is likely to be reached earlier than in one's work with the typically much more verbal type of patient whom I first described, for in that instance the patient's and therapist's more abundant verbalizations tend persistently to highlight the ego-boundaries separating the two persons from one another.

In working with the predominantly non-differentiated patient, the therapist's sense of identity as a complexly-differentiated individual entity becomes further eroded, or undermined, as he finds the patient persistently operating on the unwavering conviction, hour ofter hour, that the therapist is but an undifferentiated aspect of the whole vague mass of The Hospital, but one head of the Hydra which, in psychodynamic terms, is in actuality the patient's projection of his own poorly-differentiated hostility, but which, in the patient's tenaciously-held view, is the way the world around him really is.

Further, since the patient typically verbalizes little but a few maddeningly monotonous stereotypes, the therapist tends to feel, over the course of time, with so little of his own intellectual content being explicitly tapped in the relationship, that his richness of intellect is progressively rusting away—becoming less differentiated, more stereotyped and rudimentary. Moreover, the patient presents but one or two emotional wave-lengths at which the therapist can himself tune in, rather than a rich spectrum of emotion which calls into response a similarly wide range of feelings from the therapist himself. Thus not only the therapist's intellectual resources, but his emotional capacities too, become subjectively narrowed down and impoverished, as he finds that, month after month, his patient evokes in him neither any wide range of ideas, nor any emotion except, for example, rage, or contempt, or dull hopelessness.

This feeling-experience on his part, anxiety-provoking and discouraging though he finds it, is a necessary therapeutic development. It is necessary, that is, for him thus to experience at first hand something of the patient's own lack of differentiation; for, as in the therapy with the non-integrated patient, here again the healing process occurs external to the patient, as it were, at an intrapsychic level in the therapist, before it becomes established in the patient himself. That is, the therapist's coming to view the patient, his relationship with the patient, and himself in this relationship, all as being largely non-differentiated, is a development which sets the stage for the patient's gradually-increasing differentiation. Now the therapist comes to sense, time after time, newly-emerging tendrils of differentiation in the patient, before the latter is himself conscious of them. In responding to these with spontaneity as they show themselves, time after time, the therapist helps the patient to become aware that they are a part of him.

The nuances of newly-emerging differentiation which creep into the patient's stereotyped modes of behavior are sometimes clearly perceptible to the eye or ear; for example, a long-clenched hand may look a bit more relaxed, a fleeting smile may pass over a stonily antagonistic face, a slow and mechanical walk may momentarily reveal a flash of tripping gaiety. But there are times when a therapist can only say that he feels a new response in himself in reaction to behavior which objectively seems as stereotyped as ever. A hebephrenic laugh which has always sounded to him clearly derisive and therefore offensive, may now suddenly make him feel like crying. Or the same verbal stereotype may be sensed as conveying, on landmark oc-

casions over the passage of months, entirely different feelings from those it once conveyed. For example, a nearly mute and motionless woman used to punctuate the long silences, scores of times over the months, by saying to me, "What about the getting well?" This stereotype, which at first posed a maddening and discouraging barrier between her and myself, a barrier of conveyed reproach and hopelessness, came to be clearly translatable, on one occasion, as a warmly fond "Speak to me of love" and, on a later occasion, this overtly the same "What about the getting well?" clearly meant; "I want to have a baby by you." And a hebephrenic man has come to use the stereotyped sentence, "I understand," to convey to me, variously, the following meanings: "I am completely confused"; "My worst suspicions are now confirmed"; "Be quiet, on pain of violence"; "There, there, little idiot"; and other assorted ones.

Thus a heavy reliance upon one's intuition is a technical point which I have found useful. A second point concerns the relatively sparing use of transference-interpretations—perhaps more sparing than in one's work with the predominantly non-integrated, or fragmented, patient. In the instance of that first "type" of patient, we saw that transference-interpretations may have a specific value in fostering the patient's wholeness, his integration, by focusing his disparate personality-fragments into the context of the patient-therapist relationship. But the predominantly non-differentiated patient, who is above all trying to branch out, in his interpersonal relationships and in his intrapsychic content, beyond the immediate, symbiotic situation with the therapist, may feel his precarious new differentiation to be destroyed by premature transference-interpretations which tend to bring it all back to the relationship with his therapist—which tend, that is, to reduce divergent ramifications of meaning to this one meaning.

The third and last technical point is, like the others, a function of the growth-process I have been describing, a process which involves both patient and therapist. The patient's differentiation is fostered not only by the therapist's sensing, and responding to, an increasingly differentiated person in him, but also by the therapist's permitting his own personality-differentiation, his own complex individuality which was to a large degree already firmly established prior to his beginning work with this patient, to come more and more freely into play in the therapeutic relationship. At crucial points, for example, he must have the courage to act upon the course that his own intuition directs, in *differing* sharply with the patient—to be the person he knows himself to be and to address the person he knows to inhabit the patient's body, no matter how sharply this conflicts with the patient's own image of himself and of his therapist. Whereas it was essential earlier to allow the anxiety-arousing symbiosis to develop, now the therapist must find similar courage to determinedly help in its resolution. In asserting, increasingly, his own complex individuality, he provides the patient an increasingly clearly differentiated person with whom to identify, and over against whom to become conscious of his own separate self.

In conclusion, I wish to stress once again the large element of artificiality in the divisions which I have set up in this paper, for the sake of a theoretical exposition of phenomena which in clinical practice are usually closely intertwined. For example, when a patient says to his therapist, "I don't know, when I talk to you, whether I'm having an hallucination, or a fantasy about a memory, or a memory about a fantasy," he is evidencing in the same breath a gross impairment of both integration and differentiation.

I want to emphasize, too, that the growth-processes of integration and differentiation occur, in any prolonged and successful psy-

chotherapeutic endeavor, not only in the patient, but also to a significant degree in the therapist himself; the growth-process is a genuinely mutual one.

And lastly, the states of what I have called non-integration and non-differentiation should be thought of as not merely rather fixed *levels of maturation or regression* at which a patient exists over a long period of time, but as *flexible defenses of the ego against overwhelming anxiety.* Thus, from noticing at what moments in the therapeutic session, or at what junctures over the long course of treatment, a patient's characteristic non-integration or non-differentiation notably increases or notably lessens, we can tell when areas of particularly severe anxiety have been encountered in his personality-investigation, and chart the resolution of this anxiety as growth proceeds.

REFERENCES

1. Balint, M. Friendly expanses—horrid empty spaces. Internat. J. Psycho-Analysis, **36:** 225–241, 1955.
2. Balint, M. *Primary Love and Psycho-Analytic Technique.* Liveright, New York, 1953.
3. Bateson, G., Jackson, D. D., Haley, J. and Weakland, J. Toward a theory of schizophrenia. Behavioral Sc., **1:** 251–264, 1956.
4. Benedek, T. Contributions to the libido theory: Parenthood as a developmental phase. Presented at the March 8, 1957, meeting of the Washington Psychoanalytic Society.
5. Benedek, T. Personality development. In *Dynamic Psychiatry,* Alexander, F. and Ross, H., eds., pp. 79–113. Univ. of Chicago Press, Chicago, 1952.
6. Benedek, T. *Psychosexual Functions in Women,* Chap. 12. Ronald Press, New York, 1952.
7. Benedek, T. The psychosomatic implications of the primary unit: Mother-child. Am. J. Orthopsychiat., **19:** 642–654, 1949.
8. Freud, S. Psycho-analytic notes upon an autobiographical account of a case of paranoia (dementia paranoides). In *Collected Papers,* Vol. 3, pp. 387–470. Hogarth Press, London, 1946.
9. Hill, L. B. *Psychotherapeutic Intervention in Schizophrenia.* Univ. of Chicago Press, Chicago, 1955.
10. Jacobson, E. Contribution to the metapsychology of psychotic identifications. J. Am. Psychoanalyt. A., **2:** 239–262, 1954.
11. Jacobson, E. On psychotic identifications. Internat. J. Psycho-Analysis, **35:** 102–108, 1954.
12. Lidz, R. W. and Lidz, T. Therapeutic considerations arising from the intense symbiotic needs of schizophrenic patients. In *Psychotherapy with Schizophrenics,* Brody, E. B. and Redlich, F. C., eds., pp. 168–178. International Universities Press, New York, 1952.
13. Mahler, M. S. On child psychosis and schizophrenia: Autistic and symbiotic infantile psychoses. Psychoanalytic Study of the Child, **7:** 286–305, 1952.
14. Savage, C. Variations in ego feeling induced by d-lysergic acid diethylamide (LSD-25). Psychoanalyt. Rev., **42:** 1–16, 1955.
15. Searles, H. F. Data concerning certain manifestations of incorporation. Psychiatry, **14:** 397–413, 1951.
16. Szalita-Pemow, A. Remarks on pathogenesis and treatment of schizophrenia. Psychiatry, **14:** 295–300, 1951.

RELATION BETWEEN PARKINSONISM AND PSYCHIATRIC DISORDER

FRED A. METTLER, M.D.[1] AND ARCHIE CRANDELL, M.D.[2]

The present writers have previously enquired into what neurologic disorders are encountered in large public psychiatric institutions and to what extent (19). Under the conditions studied, the most frequent neurologic disorders (excluding the cerebrovascular disease-brain atrophy complex) were convulsive diseases, congenital or developmental abnormalities and brain injury, in that order. It was pointed out that cerebral arteriosclerosis might be considered either more frequent than convulsive disorders or, if one adopted more rigid diagnostic criteria, less common than developmental and congenital abnormalities. A special feature of the original study was the emergence of a relatively high frequency of extrapyramidal symptoms despite the fact that the study was made prior to the introduction of the so-called "tranquilizers." Such a relationship is of theoretical interest because extrapyramidal and psychiatric dysfunctions may be causally related either to each other (as has been suggested by Wernicke, 1900; Kleist, '22; and others) or, alternatively, both to some common third factor.

In order to reduce the possibility of coincidence in situations in which neurologic and psychiatric disorders are apparently connected:

1. There should be a *higher incidence and/or prevalence* (a) of psychotic disorder in persons with the particular neurologic disease under investigation, than exists in the general population and (b) of the particular neurologic disorder, in question, in psychotics than in normal persons.

2. The *configurational or temporal aspects* of the relationship between the specific neurologic and psychiatric disorders *should be of a characteristic type.*

3. If the neural and psychiatric disorders do not themselves stand in a cause-and-effect relationship the occurrence of the psychiatric and neurologic phenomena should both depend upon the involvment or disturbance of *common particular structures or functions.*

As the result of animal experimentation it is the position of one of us (17) that the striatum (that is, the caudate plus the putamen) plays an important role in the organism's ability to relate itself to its environment. Since the striatum is a part of the corpus striatum (striatum plus pallidum) it might be expected that striatal dysfunction may be a significant element in extrapyramidal disorders. Subsequently, in the course of a series of psychosurgical studies, it became possible to verify, in a subjective manner, at least, that there is a high prevalence of extrapyramidal symptomatic states in mental institutions. Kleist (11) seems to have anticipated one now well-documented (by the Belgian and Scandinavian investigators) reason why this might be; namely the linkage of extrapyramidal and mental disorders in heredodegenerative patterns. F. H. Lewy (13) and Steck (25) have called attention to the alternation of psychiatric and extrapyramidal presenting signs in the same individual, especially the metamorphosis of parkinsonian-like states into catatonic rigidity and vice versa. The well-known accessibility of some extrapyramidal motor manifestations to psychodynamic therapeutic techniques

[1] Departments of Anatomy and Neurology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York City.

[2] The New Jersey State Hospital, Greystone Park, New Jersey.

has given rise to the impression that there may be two "types" of extrapyramidal disorders—true organic varieties and pseudo-organic types which are really a kind of conversion phenomenon. That these two "types" may have something in common, namely the metabolic activity of the neurocyte, has been suggested by the experience of Medinets, Kline and Mettler, who found that the extreme rigidity of catatonic schizophrenics may be resolved by sympatholytic means (16). Not to be confused with naturally occurring associations between extrapyramidal and psychiatric signs are those iatrogenic extrapyramidal symptoms which have become so common in individuals treated with the so-called tranquilizers. Are such signs evidence of sensitivity of certain cells to drugs of an especial class or classes or are they an illustration of Critchley's observations, made in another connection, that, "Extrapyramidal signs ... may comprise a sort of 'least common multiple' of neuronic dissolution"? Since *selective* experimental damage of the striatum, in the otherwise healthy organism, precipitates difficulty in orientation it would appear not only that extrapyramidal functions may be particularly vulnerable to generalized disorder of neural function and that disorientation is due to such generalized impairment, but that striatal disability must itself impair high level coordinative function. According to a theory advanced by one of us (17), dysfunction of the striatum results in an inability on the part of an organism to maintain adequate contact with its environment (probably the only entirely satisfactory, irreducible characteristic of a psychotic process, though not of this alone). In view of this the apparent occurrence of an abnormally high prevalence of disorders of the basal ganglia among institutionalized patients, if such a distribution is based on something more than mere impression, deserves scrutiny but is the prevalence of such disorders really statistically significant and if so is it related to disturbances in particular neurologic functions or is it merely a consequence of invalidism in a society in which the psychiatric hospital is a convenient mechanism of providing care for the chronic patient? Are such abnormal psychiatric states as appear in cases of this type only coincidental or reactive, or are some actually caused by an extrapyramidal structural damage itself?

Unquestionably extrapyramidal disease is a stressing situation capable of eliciting adverse reactions, but one cannot overlook the fact that in diseases in which large portions of the corpus striatum are destroyed—as in hepatolenticular degeneration and kernicterus—ultimate deterioration of mentation and affect almost invariably occurs. In Huntington's chorea the striatum is more severely affected than the pallidum and mental deterioration also occurs, but obviously the cellular loss is not confined to the striatum. Still, we know of no neuropathologic state or case in which more than half the striatum of each side has been destroyed in which some mental impairment has not existed. Russell Meyers (21) has discussed the psychic condition of patients who had been subjected to an operative procedure for paralysis agitans in which appreciable parts of the caudate were removed together with the rostral part of the internal capsule. Most of these cases were unilateral operations. No alteration in conventional psychological tests for intelligence was subsequently observed. He has since told us that of five bilateral cases three survived. All of these exhibited high-level behavioral deficits. Clovis Vincent (26) in 1925 reported a Mme. T. who sustained bilateral striatal softening as the result of embolic showers secondary to cardiac disease. After an initial period of stupor (without unconsciousness), deviation of the head and eyes to the left and transient right hemiparesis, Mme. T. was able to live a nearly normal existence. She answered questions correctly, sewed and read the newspaper. She did not cry or laugh inappropri-

ately but it was observed that her face appeared smooth and smiling. The only intellectual deficit present was characterized by Vincent as an impairment of attention. Specifically she had difficulty in performing a series of acts in accordance with directions. It is interesting to observe, since many bilateral striatal cases have difficulty in eating, that she could not whistle, puff up her cheeks or suck up fluids with a straw and had difficulty in swallowing. In the case of animals with striatal lesions it has been found (8) that learned avoidance behavior is impaired by small lesions but that the capacity to relearn is retained. With larger lesions relearning is itself impaired and with very large lesions even unlearned avoidance patterns are interfered with.

If the hypothesis that extrapyramidal and psychiatric disorders are associated for reasons other than coincidence is correct, it should be possible to substantiate the impression that there are more cases of extrapyramidal disease—such as parkinsonism—in chronic mental institutions than can be accounted for upon the basis of chance, once other non-causal relationships, such as age or the availability of custodial care, have been considered. As soon as this was attempted we became acutely aware that relatively little quantitative knowledge is available in this area not only as to whether there are proportionally more cases of parkinsonism in mental hospitals than outside, but even on the prevalence of this condition in either the American population at large or in the large mental hospitals of this country.

This is the background of the problem which led us to investigate the question, "What really *is* the proportion of mental hospital cases which are essentially neurologic problems and what is the nature of their *actual* disability as contrasted with the impression gained from an examination of the paper record?" This is a problem dealt with in our prior publication (19). Insofar as parkinsonism and paralysis agitans are concerned, 47 such cases were found in a population of 5704 individuals (8.2/1,000). In attempting to evaluate the significance of this number we come to the necessity of arriving at a figure as to what the expectation should be for a "normal" population of 5704 individuals of comparable age. In this case we need to know:

1) What is the upper limit of prevalence of non-iatrogenic parkinson-like states in the general population?

2) What is the prevalence of non-institutionalized psychiatric cases in the sample of the general population evaluated in 1), above, and,

3) To what extent is the institutionalized population to be studied comparable (as, for example, with regard to age, sex and special liability to somatic disorders) with "normal" samples?

Some of these data are presently beyond precise determination, and a definitive correlation between such two types of population cannot be developed. The best that can be done is to see whether the magnitude of distribution of extrapyramidal manifestations is markedly different in the institutionalized population from what is encountered extramurally.

Many neurologists hold an *ex cathedra* view that paralysis agitans does not predispose toward mental disorder and Denny-Brown (5) has been widely quoted to that effect but, as one of us has previously pointed out (18, p. 13), Denny-Brown seems to have been relying on a questionable interpretation of work by Mjönes (22). Most families in which such cases exist have an equally firm conviction that the rigidity displayed by the patient with whom they are familiar is not confined to neuromuscular functions. Many psychiatrists admit that parkinsonism is unusually prevalent in mental institutions but believe that this is due to the advanced average age of institutionalized populations and that a high prevalence of parkinsonism is therefore not only associated with, but is

causally related to, cerebrovascular disease. The purist might argue, with Critchley (4, p. 204 *et seq.*), that although the aged have extrapyramidal symptoms these may not justify a diagnosis of true parkinsonism. Peculiarities in selection and distribution of data may also be involved. One reason for the institutional impression that paralysis agitans is especially common in the aged might be that cases of the disorder usually are cared for at home until the family grows up and is dispersed.

Occurrence of paralysis agitans in the general population. In order to come to a conclusion as to how common paralysis agitans is in a general population Mjönes analyzed admissions to a general clinic. The figure he arrived at was 1.6/1,000 at age 50 or over (22, p. 128). The U. S. Public Health Service mortality rate for the disease for the population at large in 1950 was 1.6/100,000 and Kurland has supplied us with the accompanying table (Table 1) for the rate of parkinsonism among persons dying in Canada (1.7/100,000). Mortality data are, of course, lower than prevalence figures. Kurland (12) encountered a prevalence rate of 1.8/1,000–1/100 depending upon age) for a small, urban community (Rochester, Minnesota). In an effort to arrive at another independent estimate of the occurrence of the disorder in a general population we have examined the figures published by Julia Bell (1) for a consanguinity study. The rate arrived at, 1.5/1,000, is in agreement with general population estimates made by both Mjönes and Kurland.

TABLE 1

Parkinsonism Deaths and Death Rates: Canada, 1951, Based on the Official Mortality Statistics

Age In Years	Category to Which Certificates Were Coded					Death Rate per 100,000 Pop.
	Underlying		Contributing No.	Complication No.	Total No.	
	No.	% of Total Number				
0–24	0	0	0	0	0	0
25–44	3	100	0	0	3	0.1
45–54	10	56	8	0	18	1.2
55–64	36	52	29	4	69	6.3
65–74	104	48	104	11	219	28.5
75+	91*	41	116	13	220	62.5
All ages	244	46	257	28	529	3.7

From Kurland (12).* Death rate based on 244 deaths is 1.7 per 100,000 population.

It is obvious that estimates such as these cannot be utilized without attention to the types of samples on which they are based. Mjönes considered his own figure too low but the agreement between his and Kurland's and Bell's data suggest that a rate of about 1.5/1,000 must be somewhere near the actual state of affairs for the general population.

Our next problem is to determine to what extent the general population contains uncommitted, mentally ill persons. Statistics available in the United States for the population as a whole, insofar as they relate to this question, can hardly be considered to be even educated guesses. According to Ekblad (6) the average figure for psychopathy in non-institutionalized Swedish males of military age is 15 per cent. This is not far from figures available from statistics available from the departments of mental hygiene of Australia (15–20 per cent) and New York State (8–10 per cent) though the latter figures are based upon the population as a whole rather than a selected age group. Fremming (7) gave the expectation for schizophrenia, manic-depressive psychosis and epilepsy in a "normal" Danish population as about 0.9, 1.6 and 0.3 per cent respectively, and pointed out that these figures were comparable with Sjögren's for a Swedish population. Sjögren (24) later observed that the psychotic population in a Swedish community could be broken down about as follows: schizophrenia, 33 per cent (with slightly more than half of these institutionalized); manic depressive, 18 per cent (8 per cent of these being institutionalized); senile psychosis, 9 per cent; presenile psychosis, 11 per cent; other diag-

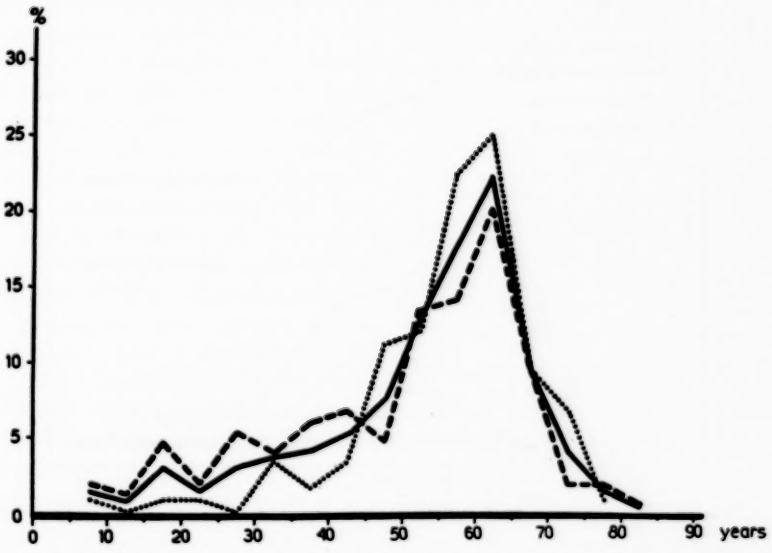


FIG. 1. Mjönes' (22, pg. 39) chart for the *age of onset* for his clinically examined cases of paralysis agitans. The different lines represent different genetic groupings of cases all of which were considered to be examples of paralysis agitans rather than parkinsonism. Mjönes concluded that the individuals in the group represented by the broken line were of hereditary origin.

noses, 16 per cent; and undiagnosed, 15 per cent. Oligophrenics were not included by Sjögren in his psychotic group. According to him there were 75 per cent as many oligophrenics as schizophrenics but only 10 per cent of the oligophrenics were hospitalized. All these figures can be fitted together in a general way and indicate that if extrapyramidal disorders are really correlated with psychiatric difficulties, and the figures of Ekblad, Fremming, Sjögren and others are meaningful, it is possible for these two phenomena to be related outside of mental institutions as well as inside, particularly if we accept Mjönes' and Kurland's conclusions that some forms of parkinsonism have a definite genetic basis or if we assume that the disorder may be an early manifestation of any general deteriorative process of the neural system.

Influence of age. Table 1 may be compared with (Figure 1) Mjönes' graph (22, pg. 39) showing the age of *onset* of the disorder in his cases. Taken together, these show that the high *prevalence* of paralysis agitans in the eighth decade begins with an *incidence* which increases rapidly from the middle of the fifth to the first half of the seventh decade. If paralysis agitans is a measure of neural deterioration, in a broad sense, it would seem that about half the number of breakdowns should already be apparent by the 65th year of age. The impression that paralysis agitans may begin as early as the sixth or fifth decades, is not merely an impression of common, indi-

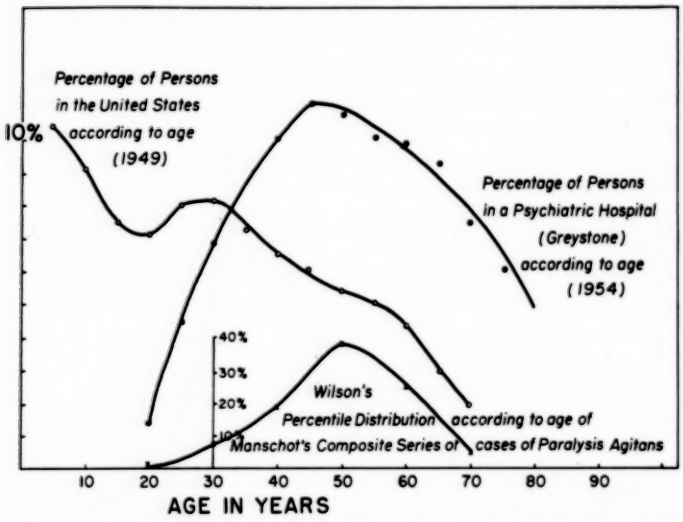


FIG. 2. Chart of age of Manschot's cases exhibiting parkinsonism shown in relation to the age distribution of all cases resident in Greystone.

vidual clinical experience but has been verified by many statistical inquiries including Wilson's (28) (see Figure 2) analysis of Manschot's (15) cases which occurred prior to the complications due to the encephalitis epidemic immediately after World War I.

Figure 2 illustrates that the population of the psychiatric institution studied falls into an age distribution of such a nature as to contain its largest number of individuals in the area in which the onset of paralysis agitans can be expected to occur. One would therefore anticipate the prevalence rate of parkinsonism to be higher in such a population than in an extramural group. The circumstances which lead to the development of a neurologic disorder, such as paralysis agitans, evidently build up to a maximum in about the same way as those which lead to psychiatric institutionalization, an observation which is consistent with Brain's assumption that extrapyramidal signs are a "least common multiple" of generalized neuronal dysfunction.

These curves indicate that the impression that the incidence of paralysis agitans increases *pari passu* with age is fallacious. Such an impression might be due to the fact that patients with paralysis agitans look much older than their chronologic age (as do psychotics). Another reason appears to be that patients are able to survive for long periods with the disease which continues to progress. Still another may depend upon what one is willing to include in the diagnosis. We did not include in the paralysis agitans-parkinson cohort such aged persons who, as Critchley says, merely show modest tremor and/or slowing of movement. If one deliberately searches for cases of paralysis agitans in geriatric institutions one encounters a special problem which complicates the interpretation of the findings. Consider the following tabulation (Table 2) of populations for several particular institutions at the close of the year 1955. Other institutions which have been studied reveal similar incomparabilities and wide span, indicating very clearly that selective factors determine the type of residents admitted. It is significant that those institutions for the aged which do not accept residents who are in ill health at the time of application for admission (about

age 64) rarely if ever encounter these disorders whereas institutions which exercise some of the functions of a chronic hospital may get very many such cases. Public institutions, other than psychiatric hospitals, which operate both as custodial homes and chronic hospitals come closest to an unselected frequency but, even here, social considerations often determine whether these cases come to reside in such an institution or in a psychiatric hospital.

Post-encephalitic type. Almost all the extrapyramidal cases in geriatric institutions are due to cerebrovascular disease or are idiopathic. This is not true of a significant proportion of the cases seen in mental institutions and in these we are thrown upon the necessity of distinguishing between postencephalitic parkinsonism, idiopathic paralysis agitans and parkinsonism due to cerebrovascular, and, to a lesser extent, other disease.

The relation between encephalitis and both neurologic residuals and psychiatric sequellae may certainly be regarded as established. According to Wilson, of the encephalitic cases involved in the epidemic of 1919 about one-half ultimately exhibited psychiatric disorder. One is justified in assuming that for every postencephalitic case in a given mental institution there should have been at least two acute cases in the community at some previous date. Calculations of this type suggest that either the diagnosis of postencephalitic psychosis must frequently be erroneous or that encephalitis is much more common than any examination of statistics from general hospitals would reveal. Probably both circumstances are true.

Since the association between encephalitis and both parkinsonism and psychiatric disorder is admitted, one would expect to find a relatively high percentage of cases of postencephalitic parkinsonism in mental institutions. Of the 47 cases of paralysis agitans in Greystone on November 5, 1956, 12 were postencephalitics and two more possibly so (25–30 per cent, as contrasted with 10 per cent in Kurland's noninstitutionalized population), three were of cerebrovascular origin, two syphilitic (?), two traumatic (?) and the remainder (26) of idiopathic or unknown origin. Of the latter, only 12 clearly fitted the traditional picture of the idiopathic type while 14 presented a picture of progressive pallidal degeneration (*i.e.* akinesia and rigidity were relatively more prominent than tremor) without pigmentary changes in the retina. No cases clearly due to carbon monoxide poisoning were detectable.

TABLE 2

Number and Percentage of Cases of Paralysis Agitans Located in Institutions for Persons 65 Years and Above in the Northeast Area of New Jersey

Institution	Age span of residents	Number of residents	Number with parkinsonism	Percentage of residents with the disorder
Actors Fund Home	65–93	21	1	5%
Bethany Home for Aged	70–97	45	0	0
Methodist Home for Aged	65+	209	25	12%
Morris County Old People's Home	65+	125	3	2.4%
Roosevelt Park Colony for the Aged	65–91	55	0	0
		455	28	6.1%

There are now two groups of recent, and therefore non-epidemic, statistics available for the relation of postencephalitic to other types of parkinsonism in a general population, those of Kurland (12) and those of Mjönes (22, p. 26). The latter author found that of 250 cases of paralysis agitans and parkinsonism, 32 could be considered of arteriosclerotic origin, 24 could be characterized as parkinsonism and 115 had no relatives with a similar disorder (*i.e.* 79 were of the "familial" type). Allowing for the fact that the search for encephalitis would be conducted more vigorously in a mental than general hospital population it

still appears that the expected, disproportionately large postencephalitic component is present in the former type of sample. Since postencephalitic parkinsonism appears in the population at an earlier age than does idiopathic it is of some interest to examine the distribution of the Greystone cases with regard to age (Figure 3).

Other infections and trauma. It is not possible to determine from available records to what extent factors such as trauma or post-traumatic infection and syphilis differ in contributing to the so-called postencephalitic cohort in mental institutions from the way in which they might with regard to postencephalitic groups not so institutionalized. Indeed it is very difficult to weigh the importance of these "causes" (9). It would seem that in the present instance unusual "causes" were peculiarly frequent. Our own impression is that where neurosyphilitics are concentrated, as in a mental institution, there is bound to be a high order of coincidentalism with known effective causes, such as encephalitis, and the same might be said for trauma except for the fact that in the "traumatic" cases noted here the extrapyramidal disorder was

Number of Cases and Median Ages of Subtypes of 44 out of 47 cases (3 arteriosclerotic) of Paralysis Agitans and Parkinsonism in a Psychiatric Hospital (Greystone) with a total population of 5704 (rate of 8.2/1000)

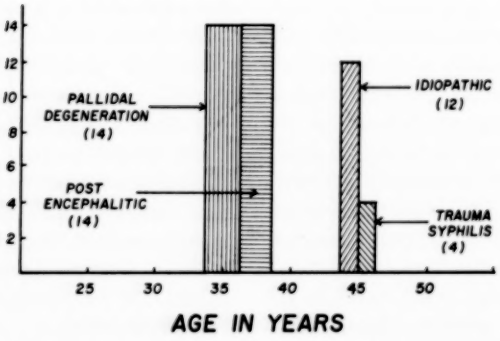


FIG. 3. Percentage of cases in the paralysis agitans complex, arranged according to age (as of 1956) and type. We are aware of the dubious nature of the attribution of paralysis agitans to trauma and that Wilson entirely discredited trauma as a cause. The two cases noted here were both atypical and may (despite the temporal association between injury and onset) have been due to infection. One case (W.C.) definitely had a chronic temporal bone infection but whether this was present before the traumatic episode is not clear. (This man seems to have been acutely ill for a protracted period immediately after an alleged "railroad bull" beating.)

The cases included under the term "pallidal degeneration" had no history of tranquilizing medication or history of infection. They exhibited loss of associated movements and resistance to passive movement but no tremor. It is not clear whether this is a separate heredodegenerative group with a low age of onset, like that described by Bell and Clark (2), or a complex belonging, in part, to the post-encephalitic and, to a lesser degree, idiopathic groups. It will be observed that while the peak for *onset of disease* in Figure 1 falls between 60 and 70 years of age, in this and the curve in Figure 2 (both of which are for *frequency of existence* of the disease and therefore after age of onset) it is much earlier, being between 45–50. If this graph had been plotted on a ten- instead of five-year basis it would have a distribution somewhat like Manschot's except for a convexity in the rising slope due to the pallidal degeneration component.

It will be observed that, since the normal rate for paralysis agitans is 1.5/1000, even the frequency of the "idiopathic" component in this sample exceeds the anticipated nine cases.

1) atypical, 2) immediately succeeded allegedly brutal head beatings and 3) the patients seem to have been acutely ill for a protracted period afterward. In one case a definite chronic osteomyelitic process seems to have been present and the clinical picture itself was of a markedly asymmetrical focal nature. One is inclined to attribute these two so-called "traumatic" cases to infection occurring as the result of trauma rather than to the trauma itself.

Heredodegenerative disorders. The familial frequency of some types of paralysis agitans has been commented upon by many writers (28). Mjönes believes his data support the hypothesis that paralysis agitans may be caused by hereditary factors operating in accordance with the principle of monohybrid autosomal dominance. Kurland similarly subscribes to a dominant (with incomplete penetrance) genetic factor for the nonencephalitic cases. Very little is known about the genetic background of any of the Greystone cases. In view of the existence of a group which presented a picture of progressive pallidal degeneration (these could not be classified as Winkelman syndrome because of the apparent age of onset and absence of pigmentary changes) it seems reasonable to assume that heredofamilial degenerative disorder of the nervous system may also make some contribution to psychiatrically institutionalized cases of parkinsonism which might, under some circumstances, be considered idiopathic.

Arteriosclerotic parkinsonism. The contribution of cerebrovascular disease, other than syphilis, to this group of 47 cases, though significant is disproportionately small. It is probable that other such cases exist in the hospital but were not found and did not get into the group of 47 and therefore do not influence considerations within that sample. The presence of such cases, while extending the distribution curve into the upper age brackets, would raise rather than reduce the prevalence rate given, since this was determined in terms of the total hospital population and not a subsidiary group. The problem of coming to a decision as to whether parkinsonism can be of arteriosclerotic origin is identical with that of coming to a decision as to whether cerebral arteriosclerosis exists, a question the present authors have previously discussed (19). For the present it may be said that cases were considered of cerebral arteriosclerotic origin only if they fulfilled the especial criteria we accepted for the existence of that disorder, *i.e.* a history of repeated neurologic disabilities with more or less complete remissions, or evidence of focal cerebral disease explicable upon the basis of middle cerebral or basilar artery thrombosis.

Psychiatric characteristics of the group. While it is true that most of the 14 postencephalitic cases had clear histories of amoral, destructive, impulsive episodes of behavior, this was not seen in the other patients in the group who were characterized instead by emotional and intellectual inflexibility rather than lability. Confronted by altered situations such patients were unable to make up their minds about embarking upon any alteration in their routine and were likely to perseverate in old established patterns, producing an appearance of rigidity where there was only an inability to make a new choice. It was this pseudorigidity coupled with depression and inaccessibility which was so frequently commented upon by their relatives and which Mjönes seems to consider a "reactive" phenomenon. These cases give the appearance of being bound to habit by less tense bonds than the truly obsessive individual and although many were irascible their irritability was diffuse rather than well directed and lacked drive. Emotional and intellectual restriction was often sufficiently marked to qualify them for Mjönes' designation as "organic" mental disorder but it may be questioned whether, in the case of two bed-ridden cases, their

somatomotor deficit was not itself the principal reason for their admission. It is easy to see why the neurologist who deals with cases like these in their early stages is of the opinion that they are not psychiatrically ill. Although often suspicious and somewhat paranoid they have no elaborate hallucinations and express no wholly bizarre ideas. One gets the impression that if one is willing to wait they will be able to produce coherent, understandable answers to most questions. On the other hand the psychiatrist who sees such cases, after the neurologist is no longer concerned about them, often wonders just when it became apparent that the inability to develop positive adaptive behavior became so severe that an environmental change had to be effected. How many other people were placed in jeopardy or actually damaged, either in motor traffic or in worldly affairs, before commitment of these patients took place?

The "pallidal degenerative" cohort exhibited a type of behavioral defect very much like that of the "idiopathic" cohort.

Whether such persons are to be considered mentally ill depends very much upon one's attitude toward what it is that constitutes mental illness—that is, whether persons who are unable, because of disordered neural function, to fulfill "normal" standards of adaptive behavior, are mentally ill or whether the term mental illness is to be reserved for those persons who are apparently not functioning as well as we would expect in terms of the neural substrate available to them. We have come far enough from the days of Diderot to recognize that defects in adaptive behavior imposed by a lack or loss of vision or hearing are very different from a hallucinative psychosis but we have not come far enough to characterize the precise differences between the mental processes of the blind and/or deaf from each other and from persons who are not deprived. To say that the adaptative behavioral deficits of parkinsonism are not those of the schizophrenic is not a certification of normalcy. Neither does the qualification of a paranoid trend, in such an individual, as reactive or of organic type wholly divorce its dynamics from the dynamics of paranoid schizophrenia.

It may be of some value to point out, in trying to define the nature of the adaptive deficit of the parkinsonian patient, that striatally injured animals exhibit a not wholly dissimilar defect (20). Thus, when lesions of significant size exist, the adaptive defect which such animals display appears to exist at some point in the sensomotor processes which lie between perception and neuromuscular effectuation. It does not interfere with the recognition of previously noxious situations and it does not block vegetative responses to such recognition. Specifically the animal appears to be unable to put into action a thoroughly efficient series of motor adjustments which quite remove it from the noxious situation or entirely terminate that situation. In the laboratory it has been postulated that the process which is interfered with by striatal lesions is one which prepares the organism for somatomotor action, and for this process, akin to the ability which must lie behind the making of a choice, the term *prohairesis* is offered.

Parkinsonian patients, though not to be regarded as suffering from primary striatal pathology and this alone, do have what may be considered a *prohairetic* defect. Of course they have other defects as well (not only at the motor level in connection with associated movement but also in autonomic function) but the striatal type of disorder is definitely detectable possibly, since the striatum discharges in part through the pallidum, as a result of blocking at the pallidal level or below. Whether striatal damage is also coupled with dysfunction in the afferent half of the sensory, associative and motor complex is not yet clear.

Obviously *prohairetic* disorder is not seen

in young postencephalitic patients who display uncontrolled behavior and emotional lability but neither do such patients show a fully devoloped parkinsonian state at that stage of the disorder.

It is perhaps much safer to say that persons with basal ganglia disorder frequently suffer from complex disorders of adaptation, which are not a direct consequence of their somatomotor defects, than to say they have a higher incidence of psychotic disorder. The latter phrase may carry too restrictive a connotation. In a series of 146 cases of paralysis agitans (some of whom were postencephalitic) Patrick and D. M. Levy (23) found that of 48 who exhibited mental symptoms such symptoms appeared before the onset of the paralysis agitans as frequently as afterward. In a series of "advanced" cases F. H. Lewy (13) encountered psychopathy in 64 per cent.

Is there any evidence of basal ganglia dysfunction in the primary psychiatric disorders? At the present time, when most of the population of a mental institution is taking drugs which are known to precipitate "extrapyramidal" symptoms, it is worth recalling that restriction of associated movement and tremor were fairly common phenomena in the psychiatric hospital of a decade and more ago. Presumably many of these cases belonged specifically to the known large organic cohort but Critchley's hypothesis may be applicable to functional as well as organic "dissolution." A small number of cases of catatonic rigidity among schizophrenics regularly display neurologic phenomena indistinguishable from paralysis agitans for a few days or weeks as they are going into or emerging from catatonic rigidity—and there is a tendency for cases of paralysis agitans to appear in families with other types of neuropsychiatric disorder (14, 22)—but the characteristic motor hallmarks of parkinsonism are certainly not common in "functional" psychotics. However, if one includes *prohairesis* among the signs of extrapyramidal damage a high percentage of functional cases can be considered to display such a defect if indeed it is not a fundamental characteristic of the schizophrenic process. Such a point of view would fulfill one requirement stated early in this paper, that if a relationship between particular neurologic and psychiatric disorders exists the relationship should be of a characteristic type.

SUMMARY

As compared with noninstitutionalized populations the rate of parkinsonism in a large mental institution has been found to be substantially higher. Several reasons appear to be responsible for this. The age distribution in a psychiatric institution is of such a nature as to parallel that of incidence of parkinsonism. There is, further, a selective tendency for postencephalitic cases to display both personality disorders and parkinsonian features. On the other hand it is probable that many aged extramural cases which are diagnosed as paralysis agitans would not be so classified in a psychiatric hospital, if the orientation suggested by Russell Brain, and supported by the newer trend in neurology in classifying cerebral vascular disorders, is followed. It is probable that many investigators would not have included some or any of the 14 cases classified by the writers as pallidal degeneration in the total of parkinsonians. If, however, one is willing to take the comprehensive view behind Bostroem's (3) classification of amyostatic symptom complex, and to concede that *paralysis agitans sine agitatione* is more than a paradoxical phrase, such cases must be included and they form a large cohort at a surprisingly young age. These cases appear to be congeners of the Hallervorden-Spatz, Kalinowsky, Winkelman and similar syndromes.

Although the age distribution of institutionalized cases definitely favors a higher prevalence of parkinsonian cases than would be encountered in a general popu-

lation which includes a typical sampling of young persons, it is interesting to observe that the "idiopathic" institutionalized cases are concentrated in the decade from 40–50 rather than in the oldest age bracket. Patrick and Levy (23) found the highest prevalence for idiopathic cases in their non-institutionalized group to be in the 51–60 year group and commented that Erb had found "private and dispensary cases" to run "along the same curve." Our own sample would not seem to fit into any hypothesis which might regard it as merely the terminal phase of noninstitutionalized cases. Also it is clear, from the dissimilar distribution of types, that ours are not merely the more severely incapacitated cases of each group, since it is obvious that there is a much greater likelihood that any given postencephalitic person will be hospitalized than will an idiopathic case. To say that the concentration of parkinsonian cases in a mental institution is merely a result of the custodial functions of such hospitals is to express a half-truth, since all but a very few of the cases examined were ambulatory and able to care for themselves within the limits of their *prohairetic* defect. It was this unadaptive aspect of their condition which seems to have brought the idiopathic cases to the hospital in the first place emphasizing that, in our present social organization and quite apart from psychiatric theory, a breakdown in the capacity to adapt effectively to environment has become a cause of commitment along with uncontrollable behavior, disordered thinking process and failures in comprehension.

REFERENCES

1. Bell, J. Determination of consanguinity rate in general hospital population of England and Wales. Ann. Eugenics, **10:** 370–391, 1940.
2. Bell, J. and Clark, A. J. A pedigree of paralysis agitans. Ann. Eugenics, **1:** 455–462, 1926.
3. Bostroem, A. *Der Amyostatische Symptomenkomplex*. Springer, Berlin, 1922.
4. Critchley, M. Neurologic changes in the aged. A. Res. Nerv. & Ment. Dis., Proc. **35:** 198–223, 1956.
5. Doshay, L. J. *Parkinsonism and Its Treatment*. Lippincott, Philadelphia, 1954.
6. Ekblad, M. Psychiatric and sociologic study of series of Swedish naval conscripts. Acta psychiat. et neurol. scandinav., Suppl. 49, 1948.
7. Fremming, K. H. *Sygdomsriskoen for Sindslidelser og andre sjaelelige Abnormtilstande i den danske Gennemsnitsbefolkning paa Grundlag af en katamnestisk undersøgelse af 5500 Personer Født i 1883–1937*. Munksgaard, Copenhagen, 1947.
8. Gomez, J. A., Thompson, R. L. and Mettler, F. A. Effect of striatal damage on conditioned and unlearned behavior. Tr. Am. Neur. A., **83:** 88–91, 1958.
9. Kehrer, F. Der Ursachenkreis des Parkinsonismus (Erblichkeit, Trauma, Syphilis). Arch. Psychiat. **91:** 187–268, 1930.
10. Kleist, K. Die psychomotorischen Störungen und ihr Verhältnis zu den Motilitätstörungen bei Erkrankung der Stammganglien. München med. Wchnschr., **69:** 412, 1922.
11. Kleist, K. Die Auffassung der Schizophrenie als psychische Systemerkrankung (Heredodegeneration). Klin. Wchnschr., **2:** 962–963, 1923.
12. Kurland, L. T. Epidemiology: incidence, geographic distribution and genetic considerations. In *Pathogenesis and Treatment of Parkinsonism, pp. 5–43,* C. C Thomas, Springfield, Ill., 1958.
13. Lewy, F. H. Die Lehre vom Tonus und der Bewegung. Monogr. gesamtgebiete Neurol. u. Psychiat., **34:** 1923.
14. Lundborg, H. *Medicinisch-biologische Familienforschungen innerhalb eines 2232-köpfigen Bauerngeschlechtes in Schweden*, 2 Vols. Fischer, Jena, 1913.
15. Manschot, G. W. *Paralysis Agitans*. F. van Rossen, Amsterdam, 1904.
16. Medinets, H. E., Kline, N. S. and Mettler, F. A. Effect of N,N-dibenzyl-B-chlorethylamine hydrochloride (Dibenamine) on autonomic functions and catatonia in schizophrenic subjects. Proc. Soc. Exper. Biol. & Med., **69:** 238–246, 1948.
17. Mettler, F. A. Perceptual capacity, functions of the corpus striatum and schizophrenia. Psychiat. Quart., **29:** 89–111, 1955.
18. Mettler, F. A. Anatomy and physiology of the extrapyramidal motor passage. Prem. Journ. Com., Prem. Congr. Internat'l. des Sciences Neurol., Bruxelles, Acta med. belg., 11–37, 1957.
19. Mettler, F. A. and Crandell, A. Neurologic disorders in psychiatric institutions. J. Nerv. & Ment. Dis., **128:** 148–159, 1959.
20. Mettler, F. A., Thompson, R. L., Hovde, C. A., Gomez, J. and Du Pree, A. L. The striatal syndrome. Tr. Am. Neur. A., **82:** 26–31, 1957.
21. Meyers, R. Dandy's striatal theory of "the

center of consciousness": surgical evidence and logical analysis indicating its improbability. Tr. Am. Neurol. A., **75**: 44–49, 1950.

22. Mjönes, H. Paralysis agitans. A clinical and genetic study. Acta psychiat. et neurol. scandinav., Suppl. 54, 1949.
23. Patrick, H. T. and Levy, D. M. Parkinson's disease. Arch. Neurol. & Psych., **7**: 711–720, 1922.
24. Sjögren, T. Genetic-statistical and psychiatric investigations in a West Swedish population. Acta psychiat. et neurol. scandinav., Suppl. 52, 1948.
25. Steck, H. Les syndromes extrapyramidaux dans les maladies mentales. Arch. Suisses neurol. & psychiat., **19**: 195–233, 1926, and **20**: 92–136, 1926.
26. Vincent, C. Foyer da ramollissement limité au noyau lenticulaire et à la tête du noyau caude. Aucun symptôme strié. Rev. neurol., **1**: 194–209, 1925.
27. Wernicke, C. *Krankenvorstellungen aus der psychiatrischen Klinik in Breslau.* Schletter, Breslau, 1899–1900.
28. Wilson, S. A. K. *Neurology*, 2 Vols. Williams & Wilkins, Baltimore, 1940.

STUDIES IN ABSTRACTION: SCHIZOPHRENIA AND ORALITY: PRELIMINARY RESULTS

JERRY M. LEWIS, M.D.,[1] E. CLAY GRIFFITH, M.D., ALBERT F. RIEDEL, M.D. AND BELVIN A. SIMMONS, M.D.

The relative inability of many schizophrenic patients to think in an abstract manner is a well-documented clinical finding. One method of measuring this impairment has involved the interpretation of proverbs as demonstrated by Benjamin (3) and more recently by Gorham, (5) Elmore and Gorham (4) and Becker (2). The latter workers have shown in well-controlled studies that the differences between schizophrenic patients and control subjects are independent of intellectual differences between the groups.

Arieti (1) has suggested that the relative loss of abstract ability of schizophrenic patients is a cardinal manifestation of such patients' retreat from Aristotelian logic to a more primitive form of thinking. As such, the loss of abstract ability can be conceptualized as an attempt to minimize anxiety. Psychogenic theories regarding the etiology of schizophrenia place great emphasis upon the early nature of the anxiety-producing trauma; that is, the first year or so of life. If such theories are valid then schizophrenic patients might well demonstrate greater difficulty abstracting proverbs, the latent content of which is concerned with early developmental experiences as contrasted to proverbs having to do with later experiences. Stein and Ottenberg (7) have used the psychosexual stages of development as a frame of reference in olfactory studies in bronchial asthma. Borrowing this frame of reference, this paper deals with preliminary data investigating a presumed relationship between the content of the proverbs and the inability of schizophrenic patients to interpret abstractly. Proverbs with oral, anal and phallic latent content were utilized in order to explore the hypothesis that schizophrenic patients have more difficulty abstracting oral material than they do anal or phallic material.

[1] Department of Psychiatry, Southwestern Medical School of the University of Texas and Timberlawn Sanitarium, Dallas, Texas.

METHOD

Operational definitions of oral, anal, phallic and undifferentiated proverbs were formulated by the authors. Oral proverbs were defined as those basically referring to the mouth, oral cavity or symbols thereof and activity such as eating, drinking and talking. Anal proverbs were defined as those basically referring to the anus, anal excretory functions and symbols thereof and including such derivatives as cleanliness and uncleanliness, possessiveness, frugality, money and sadism. Phallic proverbs were defined as those basically referring to the genital organs and symbols thereof and including such derivatives as love, romance and coitus. Undifferentiated proverbs were defined as those basically not referrable to the oral, anal or phallic phases of psychosexual development.

Proverbs which filled the operational definitions were obtained from a standard dictionary of proverbs (6), and fifty such proverbs were presented to three independent judges; a psychologist, psychiatrist and psychoanalyst. The judges were given the operational definitions and instructions to categorize each proverb on the basis of its latent content. Only those proverbs in which complete inter-judge agreement was obtained were used in this study. Sixteen such proverbs, four from each of the four categories, oral, anal, phallic and undifferentiated, were presented

to ten schizophrenic patients and ten control subjects. Their verbatim responses were obtained and utilized in the construction of a multiple choice format for the test.

The sixteen proverbs each had four possible interpretations; a completely abstract, a partially abstract, a concrete and an irrelevent one. Judgments about responses were made by the authors following familiarization with the scoring systems of Gorham (5) and Becker (2) and after considerable study and discussion of each response. A three-point scoring system was used, with two points given for a completely abstract response, one point for a partially abstract and and no points for concrete or irrelevant responses. Total scores were recorded for abstract, concrete and irrelevant responses as well as oral, anal, phallic and undifferentiated subscores. The final test form was a paper and pencil test of the multiple choice variety. An example of each category of proverb now follows:

Oral Proverb:

There is many a slip 'twixt the cup and the lip.

———Many slips occur between the initiation and the completion of an act.

———Intentions do not always lead to accomplishment.

———The cup may slip before it reaches the lip.

———Cleanliness is next to godliness.

Anal Proverb:

It's a dirty bird that fouls her own nest.

———It is dark at night and light in the day time.

———One who does not care for his own possessions cannot be trusted with those of others.

———A dirty bird's nest is always dirty.

———Pride of ownership is often an index of character.

Phallic Proverb:

There is no eel so small but it hopes to become a whale.

———Everything is fair in love and war.

———Ambition is universal.

———High hopes are not dependent on size.

———Every eel wishes he could be as large as a whale.

Undifferentiated Proverb:

Being on sea, sail; being on land, settle.

———Do not settle on the sea and sail on land.

———One's geographical position should influence his behavior.

———The stars are high in the sky.

———Actions should be appropriate to any circumstance.

The test was presented to thirty patients, consecutive admissions to a private psychiatric hospital who fulfilled rigidly defined characteristics of a schizophrenic disorder. These included the detection during a psychiatric interview of the four so-called basic symptoms; difficulty in associations, autism, ambivalence and flattened or inappropriate affective responses. Secondary symptoms of delusions and hallucinations were present also in nineteen of the thirty subjects. Patients with doubtful diagnoses were not used in this study and several patients had to be excluded because they were too disturbed to comprehend or cooperate. Diagnostic sub-types included paranoid (N_{12}), paranoid and catatonic (N_7), undifferentiated (N_7), catatonic (N_3) and schizo-affective (N_1). The mean length of illness dated from the onset of symptoms was 4.4 years (± 5.05). The median length of illness was three years and the range of the group from one month to eighteen years. The test was administered prior to any treatment and standard instructions were utilized. The instructions informed the subjects that the test was one which investigated the way different people think and

they were asked to select the most general response or interpretation for each proverb.

The test was administered to ninety control subjects, basically a non-screened group of people; Sunday school participants, nurses, friends and others. One large group of subjects received the test in a group setting. Thirty were selected from the control group who most closely matched the schizophrenic population insofar as age, sex and education were concerned. This selection was made without reference to the test performance of the control subjects. The results presented are based on the data obtained from the thirty schizophrenic patients and the matched group of thirty control subjects.

RESULTS

The general characteristics of the two groups are presented in Table 1. The data for age and educational level were analyzed by *t* tests for correlated groups, and the analysis yielded no significant differences between the schizophrenics and controls on these variables. The distribution of males and females in each group, under the conditions of matching, was as close to equal as possible.

Table 2 shows the means, *t*s, and the probability values for the two groups on the three categories scores; abstract, concrete and irrelevant, as well as the three content scores; oral, anal and phallic. From this it will be noted that the schizophrenic patients differed from the controls on all scores except the irrelevant category. These differences were highly significant statistically.

In order to test the hypothesis that schizophrenics have greater difficulty abstracting oral proverbs than anal or phallic ones, and that this difference does not appear between the content scores for the controls, the data for each group were subjected to a single classification analysis of variance for repeated measures. Table 3 summarizes the results of each analysis and indicates confirmation of the hypothesis under study. There are highly significant differences in the content scores for the schizophrenic group whereas the data for the control group do not reveal significant differences. Study of Table 2 reveals that that source of the differences in the patient group is the low mean oral content score. The *t* tests for oral-anal and oral-phallic differences were significant at the .01 level of confidence for the patient group. The undifferentiated subscore was contaminated

TABLE 1

Mean Age, Educational Level and Sex Distribution for the Schizophrenics and controls

	Sc (N30)	Cs (N30)
Mean Age	31.7 ± 9.01	33.6 ± 7.17
Mean Education	12.8 ± 2.63	13.5 ± 2.38
Male	13	14
Female	17	16

TABLE 2

Mean Scores, t and Probability Values for the Schizophrenics and Controls

Score	Sc	Cs	t	P
Abstract	17.3	22.0	3.95	<.001
Concrete	3.1	1.0	3.50	<.001
Irrelevant	0.7	0.3	1.67	>.10
Oral	3.77	5.54	5.63	< 001
Anal	4.73	5.86	3.00	<.003
Phallic	4.80	5.70	2.16	<.05

TABLE 3

Summary of Analysis of Variance Between Content Scores for Each Group

Schizophrenics

Source	d.f.	Ss	Ms	F
Between Ss	29	263.10		
Subscore	2	20.07	10.03	7.38*
Error	58	78.93	1.36	

* Significant p .005

Controls

Source	d.f.	Ss	Ms	F
Between Ss	29	81.96		
Subscore	2	2.02	1.01	.9361*
Error	58	62.65	1.08	

* Not significant

by one of the four proverbs which both control subjects and patients could not abstract. The difficulty level of this proverb was incompatible, therefore, with that of the other fifteen proverbs. As a consequence the undifferentiated subscore mean will not be considered in this preliminary report. The inclusion, however, of this proverb in the total abstract score does not effect the significant difference between the means for patients and control subjects.

DISCUSSION

The confirmation of previous studies in regard to the relative impairment of abstraction in the schizophrenic group as compared to the matched controls was not unanticipated. It is interesting to note that significant differences were demonstrated between the two groups for all three areas of content; oral, anal and phallic. These differences were most pronounced for the oral material, somewhat less for the anal and least for the phallic. It is apparent that the abstraction impairment of the schizophrenic group is more severe when such patients are attempting to deal with material from earlier developmental experiences. The control group did not demonstrate any significant differences in abstraction ability insofar as these three areas of latent content were concerned. The finding that highly significant differences were manifested by the schizophrenic group and that such differences in differential abstraction ability substantiated the basic hypothesis under investigation is felt to be of considerable importance. These results are consistent with clinical hypotheses regarding the importance of early experiences in the etiology of schizophrenia. It is suggested that such findings also lend validity to the clinical concepts of the psychosexual phases of development.

At the present time this method of investigation has been extended into other areas. A much larger group of schizophrenic patients has been studied and data is being analyzed which explores the hypothesis that anxiety centering about unconscious oral conflicts is the intervening variable in the specific oral abstraction deficit. The test has been presented also to other groups of patients in an effort to demonstrate possible abstraction deficits in specific areas of predictable latent content. A number of studies attempting to correlate performance in this test with other psychological indices in schizophrenic patients, patients with other psychiatric disorders and college students are nearing completion.

SUMMARY

The abstraction ability of thirty schizophrenic patients and thirty matched control subjects was studied by use of a proverbs test. The relative inability of schizophrenic patients to abstract such proverbs was confirmed. The patient group demonstrated significant impairment in abstracting oral as compared to anal and phallic proverbs. No such differences were demonstrated by the control group. It is felt that these findings are consistent with psychogenic theories concerning the etiology of schizophrenia. Further studies are indicated and are in progress.

REFERENCES

1. Arieti, S. *Interpretation of Schizophrenia.* Brunner, New York, 1955.
2. Becker, W. C. A genetic approach to the interpretation and evaluation of the process-reactive distinction in schizophrenia. J. Abnorm. & Social Psychol., **53:** 229–236, 1956.
3. Benjamin, J. D. A method for distinguishing and evaluating formal thinking disorders in schizophrenia. In *Language and Thought in Schizophrenia,* Kasanin, J. S., ed., pp. 65–88. Univ. California Press, Berkeley, 1944.
4. Elmore, C. M. and Gorham, D. R. Measuring the impairment of the abstraction function with the proverbs test. J. Clin. Psychol., **13:** 263–266, 1957.
5. Gorham, D. R. Use of the proverbs test for differentiating schizophrenics from normals. J. Consult Psychol., **20:** 435–440, 1956.
6. Kin, D., ed. *Dictionary of American Proverbs.* Philosophical Library, New York, 1955.
7. Stein, M. and Ottenberg, P. Role of odors in asthma. Psychosom. Med., **20:** 60–65, 1958.

THE EFFECT OF TRANQUILIZING DRUGS AND REHABILITATION ACTIVITIES ON WARD BEHAVIOR[1]

ALFRED E. GOLDMAN, PH.D.[2] AND HAROLD S. ZAMANSKY, PH.D.[3]

The present experiment attempts an evaluation of the effectiveness of tranquilizing drugs for chronic mental hospital patients in relation to the general therapeutic setting in which the drugs are administered. While attention has been focussed, in the literature, upon the merits of tranquilizers *per se* (*e.g.*, 1, 2), little consideration has been given to the total psycho-sociological context in which the drugs are prescribed. If, as has been suggested, these drugs are most effective in association with other modes of therapy, then it would appear that the events preceding or coincident with a drug therapy program warrant serious attention.

In the present study, the effectiveness of tranquilizing drugs in the context of two particular therapeutic settings was studied. Two individually matched groups of chronic functionally psychotic women constituted the subjects of the experiment. One group (referred to as the Rehabilitation-Drug group) received a regimen of tranquilizing drugs immediately following the termination of an intensive program of rehabilitative therapy, which had been running for a little over a year.[4] The second group of patients (the Drug Alone group), received tranquilizing drugs in the context of the usual course of events on the chronic female service of a large metropolitan mental hospital.

PROCEDURE

Each of the two experimental groups consisted of 15 women. All were patients in a large metropolitan state hospital, and all had been diagnosed as functionally psychotic (*i.e.*, one of the schizophrenias or one of the affective disorders). The ages of the subjects ranged from 20 to 60 years (mdn = 38 years), and they had been hospitalized from two to 18 years (mdn = 6 years). Their formal education varied from two to 15 years (mdn = 10 years). Sixty per cent were not and had never been married.

An attempt was made to match the patients in the two groups, in pairs, on the following variables: diagnosis, marital status, intelligence, number of years hospitalized, age, severity of present illness, level of prehospitalization achievement, physical condition, years of education, prognosis, age at first hospitalization, and amount of individual and group psychotherapy recently received. Each of these variables was selected because of its potential prognostic significance. After the two experimental groups had been established, an analysis of the distributions of each of these variables revealed that individual matching had successfully been accomplished in terms of pre-established limits, on eleven of the thirteen variables. Matching failed only in age at first hospitalization and amount of group psychotherapy recently received.

[1] The research reported here was undertaken by the Pilot Study in Rehabilitation and Rehabilitation Personnel, Boston State Hospital and Harvard University School of Public Health, and was supported by a special grant from the National Institute of Mental Health.

[2] Norristown State Hospital, Norristown, Pennsylvania.

[3] Northeastern University, Boston, Massachusetts. The authors wish to express their indebtedness to Dr. Ralph Notman, Director of the Pilot Study in Rehabilitation, for his aid in many phases of this research. Thanks are also due Dr. Paul Rhudick for his contribution to the data. The cooperation of Smith, Kline and French, Ciba, and the Riker Corporation in making drugs and placebos available is also gratefully acknowledged.

[4] This program will be described in detail in Notman and Williams (4).

Immediately prior to the initiation of the present experiment, the members of the Rehabilitation-Drug group had been part of a group of 40 female patients who were exposed to an intensive program of rehabilitation activities for a period of 14 months. This larger group was selected to represent a random sample of chronic functionally psychotic females who, in the opinion of either the ward physician or the service chief, seemed likely to benefit from a program of rehabilitation therapies. This program included recreational, occupational, educational and hospital-industry therapy, vocational guidance, psychiatric social service, and, in some cases, group psychotherapy. The members of the Drug Alone group were selected from a second group of 40 patients who had served as controls in the prior rehabilitation study. With the exception of a few who received group psychotherapy, these patients were not given any special treatment, and were merely exposed to the usual course of events on the chronic female service.

In both the rehabilitation experiment and the present drug study, the experimental patients lived together on a single ward, while the controls, partly to protect their anonymity, remained scattered throughout the various chronic female wards.

Two kinds of drugs were administered in the present experiment: chlorpromazine and reserpine. Because of the small sample size, no attempt was made to distinguish between the effects of the two drugs; they will, therefore, be subsumed here under the collective term "tranquilizing drugs."

Dosage and type of drug was prescribed for each patient in the Rehabilitation-Drug group by the ward physician or service chief, and was duplicated for the corresponding member of the Drug Alone group.

The relative homogeneity of the patients within each group made it possible to prescribe, with a few exceptions, the same dosage for patients receiving the same drug. All but two pairs of patients on chlorpromazine received 100 to 200 mgs. per day and all but one pair of patients on reserpine received 3 mgs. daily. For patients in both groups this level was considered the recommended standard dosage and no patient received a drug which was not considered by the chief of service and prescribing physician as appropriate in kind, amount and duration in terms of the patient's severity and course of illness. By current practice these dosage levels were quite conservative.

Figure 1 summarizes the various treatment conditions and evaluation points employed. Patients received drugs for varying periods of time up to 10½ months (mdn = 10 mos). All but one pair of patients on chlorpromazine received the drug for 10 to 10½ months (mdn = 10.25 mos). The duration of drug administration for the reserpine patients varied from four to 10 months (mdn = 6 mos). Duration of drug administration was the same for each pair of patients. Following the drug administration period, all patients were given placebos for a period of six weeks. Since the placebo tablets were identical in appearance with the active drug pills, not only the patients, but also ward personnel were unaware of the shift from the genuine to the substitute tablets. After six weeks, the placebo was withdrawn and no tablet was given for an additional six-week follow-up period.

As the criterion of response to the various portions of the treatment program, a ward behavior rating scale, constructed by the authors, was employed. This scale consisted of 31 items, covering such behavioral areas as cooperativeness, assaultiveness, with-

DRUGS			Placebo	Withdrawal
Mdn = 10 months			6 wks.	6 wks.
A	B	C	D	E
Pre-test	Interim	Post-test	Post placebo	Post withdrawal

FIG. 1. Sequence and duration of treatment conditions and evaluation points.

TABLE 1
Median Ward Behavior Scores and Ranked Analysis of Variance

	A Pre-drug	B Interim	C Post-drug	D Post-placebo	E Post-withdrawal	χ^2_r	p	Significance among conditions*
Rehabilitation-Drug	56	52	45	43	43	23.3	$< .001$	A/CDE, B/CE
Drug Alone	54	54	52	45	48	5.15	$> .20$	

* See text for explanation of symbols.

drawal, personal tidyness, social relationships and participation in ward activities.[5] Each item was scored on a four-step continuum, so that the possible range of total scale scores was from 31 (minimum degree of pathology) to 124 (maximum pathology).

By means of this criterion, the effects of the experimental program were assessed at five points, as indicated in Figure 1: 1) a pretest, before any drug was administered; 2) three months following the initiation of drug therapy; 3) at the end of the drug administration period; 4) following the six weeks placebo period; and 5) following the six weeks period in which neither drug nor placebo was given.

The ward behavior ratings were completed by the nurse or attendant who was most familiar with any particular patient during a given evaluation period. While the raters of Rehabilitation-Drug patients were aware that these people had previously been part of the rehabilitation study, they believed that the patients had ceased to be of central experimental interest. The raters of Drug Alone patients had never[6] been aware that these individuals had served as controls in the previous rehabilitation study, and had no knowledge of the fact that any comparison between these and any other patients was intended.

Since the criterion of therapeutic effectiveness was modification in general ward behavior, it was necessary to determine the degree of similarity displayed on this variable by the two treatment groups just prior to the initiation of the drug program. An analysis[7] of the initial ward behavior ratings for the two groups revealed no statistically significant difference ($p = .27$), and suggests, therefore, that initially there were no marked systematic differences in degree of disturbance between the two groups.

RESULTS

Because of a tendency for the ward behavior rating scores to yield skewed distributions, the data of the present experiment were analyzed by means of nonparametric (distribution-free) statistics.

In the treatment of the data, both intra- and intergroup differences were evaluated. In the former case, the total pattern of changes at the various evaluation points was assessed for each group independently by means of the Friedman Ranked Analysis of Variance technique (Mosteller and Bush, 3). If the overall variance was found to be significant, then the significance of the difference between each of the possible pairs of evaluation points was assessed, by means of the Link-Wallace Method of Allowances (3). Intergroup differences were evaluated by determining the significance of the difference between the two groups of patients in the amount of change from one evaluation point to another; for this analysis Wilcoxon's Matched-pairs Signed-ranks Test was used.

The results of the first analysis are summarized in Table 1. In considering columns A through E, which list the median ward behavior scores achieved by each group at each evaluation point, it should be kept in mind that the magnitude of scores is in-

[5] Preliminary attempts to assess the reliability of this scale, using a sample of 80 chronic mental hospital patients, have indicated a correlation coefficient of .74 between the ratings of two raters who were equally familiar with the patients and the rating scale.

[6] Established by interviews with raters at the conclusion of the experiment.

[7] Wilcoxon's Matched-pairs Signed-ranks Test (Mosteller and Bush, 1954).

versely related to improvement in ward behavior. The column labelled x^2r lists the Friedman Ranked Analysis of Variance statistic, which is evaluated as chi-square, with degrees of freedom equal to one less than the number of evaluation points (in the present case, d.f. = 4).

As Table 1 indicates, overall differences among the various evaluation points for the Rehabilitation-Drug group were statistically significant ($p < .001$), whereas this was not the case with the Drug Alone group. The pattern of response of the Rehabilitation-Drug group was one which reflected progressive improvement in ward behavior throughout the drug administration period, and then, behavior which was maintained at the improved level throughout the placebo and withdrawal periods.

The final column of Table 1 indicates the results of the assessment of the significance of differences among the various pairs of evaluation points for the Rehabilitation-Drug group. If the five evaluation points are labelled A through E, this analysis indicates that improvement at a statistically significant level ($p = .05$) was obtained in comparing A with C, D, and E, and in comparing B with C and E. No significant comparisons were evident in C through E; *i.e.*, within the period covered from the post-test through the post-withdrawal evaluation. Since the BC comparison was statistically significant, while that for AB was not, it appears that the period from three months to the end of the drug administration program is an important one. Here, apparently, major gains were made. Marked improvement in ward behavior produced by the combination of rehabilitation services and drug therapy is, thus, not to be expected during the early months of treatment. Furthermore, the absence of significant changes during the placebo and withdrawal periods suggests that removing the active drug does not lead to an impairment in the previously attained level of ward adjustment, at least over the period covered by the present study.

In the assessment of intergroup differences, the significance of the difference in the amount of change demonstrated by the two treatment groups over each of the various pairs of evaluation points was determined. The results of this analysis indicated that the Rehabilitation-Drug group achieved a significantly greater gain ($p < .01$) in ward behavior than did the Drug Alone group in intervals AC and AE (*i.e.*, from the pretest to the post-test, and from the pretest to the post-withdrawal evaluation). The remaining comparisons did not demonstrate a statistically significant advantage for either treatment group.

The results of the intergroup comparisons parallel, in general, those of the within-groups analysis: by the end of the active drug period, the Rehabilitation-Drug group was functioning in a significantly superior manner to that of the Drug Alone group. Furthermore, this superiority was still apparent twelve weeks later, at the post-withdrawal evaluation.

DISCUSSION AND CONCLUSIONS

The principal finding of the present study is that female functionally psychotic patients who received tranquilizing drugs in conservative dosages, following exposure to a one-year intensive rehabilitation program, showed greater relative improvement in general ward behavior than did matched controls who received drugs without such prior exposure. The fact that this improvement was maintained throughout the placebo and withdrawal conditions suggests that these gains were sufficiently stable to resist reversal when the active pharmacologic agent (and later, the tablet itself) was removed.

It appears, at least for this patient population, and for these drugs, dosages, and durations, that the drugs alone did not effect general ward behavior in a clearly demonstrable fashion. The prior study of the effects of intensive rehabilitation services failed to produce significant improvement in the ward behavior scores of the 15 patients

in the Rehabilitation-Drug group. It seems unlikely, therefore, that the gains made by these patients in the present investigation could be attributed solely to the effects of the previous rehabilitation program. The more likely conclusion is that the present gains are attributable to the interaction between the tranquilizing drugs and the prior rehabilitation program.

This conclusion, therefore, suggests that tranquilizing drugs contribute principally to the progress of mentally ill patients by facilitating a more effective use of whatever personal or environmental resources are available to these patients.

Further attention by the therapist and researcher to the total psycho-sociological context in which drugs are administered is clearly necessary. Studies which view drugs as an isolated treatment event ignore this context, as well as what may be a crucial interaction between it and the pharmacological effects of the drug.

SUMMARY

This study attempted to assess the influence upon general ward behavior of tranquilizing drugs administered immediately following a one-year program of intensive rehabilitation services, as compared with changes effected by drugs administered in the context of the usual chronic mental hospital setting. The results indicated that the Rehabilitation-Drug group improved significantly more than the Drug Alone group, and maintained its level of improvement following the withdrawal of the drugs. It was suggested that tranquilizing drugs effect behavioral improvement by facilitating a greater utilization of environmental resources by the patient.

REFERENCES

1. Barsa, J. A. and Kline, N. S. Combined reserpine-chlorpromazine in treatment of disturbed psychotics. A. M. A. Arch. Neurol. & Psychiat., **74:** 280–286, 1955.
2. Barsa, J. A. and Kline, N. S. Treatment of two hundred disturbed psychotics with reserpine. J. A. M. A., **158:** 110–113, 1955.
3. Mosteller, F. and Bush, R. R. Selected quantitative techniques. In *Handbook of Social Psychology*, Lindzey, G., ed., pp. 289–334. Addison-Wesley, Cambridge, Mass., 1954.
4. Notman, R. and Williams, R. N. Psychiatric rehabilitation in a state mental hospital. A report of a pilot study. In preparation.

A CASE OF FETISHISM TREATED WITH LYSERGIC ACID DIETHYLAMIDE

J. D. A. WHITELAW, M.B.[1]

In previous papers (9, 10) the author and his colleagues have described the treatment of a series of patients with lysergic acid diethylamide in general terms. This paper describes the detailed treatment of a case of fetishism in a male patient. Abramson (1) describes the use of lysergic acid diethylamide (hereafter LSD) as an adjunct to psychotherapy in a case showing resistance to further analysis. He used LSD for one four-hour interview, but there does not appear to be any reference in the literature to a case treated throughout with the aid of LSD.

The patient, aged 33, presented himself in May, 1955, with the principal symptom that he had married in December, 1954, and that the marriage had remained unconsummated.

History of Complaint. For many years the patient had been attracted by mackintoshes and other rubberized clothing, *e.g.* golfing trousers. At the age of five he refused to wear a rubberized mackintosh and he was locked up as punishment; while locked up for this and other offenses he developed the practice of tying himself up. At the age of 11 or 12 he began to wear a mackintosh in bed and to tie himself up, causing perspiration and discomfort. This behavior was associated with masturbation.

In later years he was attracted by women's mackintoshes, rubber aprons and golfers' clothing which excited him when worn against the skin and under normal garments. The sound of the rubber gament and particularly the smell attracted him. Since his marriage he had worn rubber garments in his wife's presence without satisfaction and with feelings of guilt.

In sexual relationships with his wife he was impotent.

Personal History. The patient had been an only child, shy, with individual friends but unable to enjoy a group. He was educated at a private preparatory school and, later, at a grammar school. He obtained matriculation exemption at the age of 16 and had a university education with a pass degree in Civil Engineering in 1942, but he was dissatisfied and felt he should have taken a degree in languages.

He was employed in Great Western Railway Engineer's Office until 1946 when he left to accept employment as a teacher. Self-taught, he passed the intermediate B.A. in Latin, French and Russian. Since 1951 he has been teaching mathematics and engineering at a technical school.

The patient's father, now retired, had been a reporter. The father is described as an intelligent, self-taught man, an atheist, of wider interests than the mother. An irascible man with little interest in his son, he has admitted that his first reaction to the child was that he was a competitor. The patient's mother, herself an only child, had a strict religious upbringing and is now interested solely in the home and the patient.

Examination of Patient. In examination he impressed as being an intelligent man, acutely aware of his need for treatment. In discussion it emerged that his languages had some fetish quality for him in that he studied languages fanatically when his everyday work proved unsatisfactory. He was aware

[1] Powick Hospital, Near Worcester, England. I am indebted to Dr. Sybil Crane for administering the matrices and Rorschach tests and interpreting the findings, to Dr. A. M. Spencer, Medical Superintendent and Dr. R. A. Sandison, Deputy Medical Superintendent, both of Powick Hospital for their helpful comments, and to Sandoz Products Ltd., who have supplied the LSD.

of his inadequacy as a schoolmaster in being unable to maintain discipline and keep the attention of his students.

On the progressive matrices he was found to be of superior intelligence, being above the 75th and below the 90th percentile. Personality was assessed from the Rorschach test, the report of which was of interest in a number of respects. His poor ego strength, together with little capacity for personal relationships and little contact with the outside world, were reported as being in accord with his inability to join group activities. The reference to an apparent importance of tactile sensation, *e.g.* 'feeling' the spine in Card IX, is of interest in view of his fetish. The patient's reporting of male characteristics in Cards II and VI may be interpreted as suggesting underlying homosexuality.

Diagnosis. The diagnosis was made of fetishism with masochism, to be treated by psychotherapy assisted by LSD. The technique of administration of LSD has been described in the previous papers (9, 10). The patient was given LSD on 32 occasions, mainly weekly, between May, 1955, and March, 1956, in doses usually of 100–125 micrograms. The number of LSD sessions, in this case, was less than average for such a case and the dosage required to produce satisfactory response was less than has often been found necessary.

COURSE OF TREATMENT

Under treatment a mood of self-examination was induced with occasional hallucinations and alteration of body image and, later, with some relevant dreams. On numerous occasions he reported that he regarded his wife as a mother on his return from treatment.

Early in treatment the patient became very critical of himself, feeling that his sexual perversion had sapped his confidence, but his progress in studying languages gave him the necessary pride in achievement to continue living, so that the languages had themselves become a solace to him.

In common with several other patients treated at this hospital, he had a re-birth experience, feeling that he was once more in his mother's womb and had a barrier to penetrate to enter a new world where his fetish did not exist.

In subsequent treatments he referred again to this barrier. He described it as preventing him "from feeling the love of another and from even imagining the association between sexual intercourse and the orgasm—between the physical act and the emotions associated with it. I realized I had turned inwards to myself feelings which should have been turned out-wards toward another or others."

He ascribed his lack of confidence to the absence of the security of love in his parents' home, and described his fear of his father who was dogmatic and bullying.

After three months of treatment, he reported two dreams of some significance. In the first he was with his mother buying a mackintosh sleeping bag. In the second he and his wife were together in a mackintosh sleeping bag.

During the fourth month of treatment, he had an LSD experience in which he was in a room where was seated a wise and kind old man. His wife was present and he identified the kind old man "as the father of my wife and myself and of us all." He seemed to see his wife begging her "father" to make him fit for her as she had tired of waiting.

In the following month he had a hallucination of a hand emerging from a black rubber sleeve like a motor cyclist's, and it stimulated him to examine the development of his fetish. He recalled a stage in early childhood when pleasant emotion was aroused when he was deprived of comfort by being tied up or locked in an uncomfortable place.

With the later "mackintosh" stage began a preference for motor cyclist's garments and he had a mackintosh of this material at about the age of five. He recalled trying to tie himself to a door handle by the belt of this garment. Later developed his fascina-

tion for women's mackintoshes with rubberized linings.

Later in the same month while under LSD, the patient remembered having a white rubber doll given to him at about the age of one (this information was later confirmed by the mother). He used to cuddle it at night. Later, people wearing rubberized mackintoshes became important as "rubber people" and he, having a similar mackintosh at an early age, similarly became a "rubber person." The patient commented, "I would associate this material (rubber) with being deprived of my mother at night and found consolation in the doll."

During treatment he developed an insight into his lack of success in teaching. He realized that his lack of confidence could be overcome and that he could take more interest in his work as it was of use to others. His new attitude to teaching was invested with emotion and seemed not merely the result of an intelectual exercise.

In a strong reaction to LSD in January, 1956, he compared his past life with the fetish, and his creative life with his wife. He felt loathing for the fetish for the first time and "wished to destroy the person who worshipped it." Later he felt he had integrated this person into his new self.

In the following month he gradually became aware of his need for his wife, having been previously preoccupied with the need for his mother, and the fact that this need was mutual and excluded his fetish. Previously he had described a feeling of guilt when sleeping with his wife. He steadily developed awareness of having given up the struggle with reality from an early age. He had failed in face of difficult circumstances and withdrawn into his artificially created world.

In March, 1956, the patient noticed a woman wearing a glistening white mackintosh in the street. He thought that his original attraction had been to something smooth and glistening and this suggested either his mother's nipples or the nipple of a nursing bottle. He remembered the attraction that the sheen of a mackintosh had for him at the age of three or four, which was confined, at that time, to garments rubberized on the outside which glistened especially in the rain.

Later in the same month he had an LSD experience which brought in the gratification, to the extent of orgasm, which he achieved from tying himself up or by imagining himself tied to something. The pleasure seemed to arise from feeling himself utterly at the mercy of someone or something. Sometimes the thought consisted of imagining himself being confined hopelessly in a very small space into which he could just fit.

PROGRESS

Drug treatment was stopped at this stage as it seemed that all the relevant material had emerged, and the patient was given an account of the phases of sexual development. The fetish significance and the pleasure in restriction was discussed and explained in relation to the oral phase of development and infancy. His impotence was elaborated in the context of the Oedipus situation. The patient seemingly accepted the explanation and his first reaction was of satisfaction with the insight he had gained into himself. Progress in achieving sexual intercourse with his wife was slower, as she developed some negative feelings toward intercourse at this time. She was unable to correlate sexual intercourse and love, and her disgust was increased by some clumsy attempts on the patient's part.

This failure caused the patient to revert for satisfaction to his languages which he studied for several hours a day; he did not actively return to his fetish, however.

Over the next four months his wife's health was poor and he did not achieve penetration until September, 1956. In the following month he dreamed that he wished he was married to his mother and that only his father prevented this desire from being a

fact. He also dreamed that he was attired in his fetish in bed, a bed with sheets of rubber. Then his mother got into bed with him, at which point he had an emission and awoke.

At about this time he associated the smell of warm milk with that of mackintosh and when attempting intercourse with his wife, on one occasion, he had the feeling that it was his mother he was with and that he must not attempt penetration. This feeling was, of course, sharply inhibiting.

Early in December, 1956, penetration with increasing satisfaction to both the patient and his wife was again achieved. He still dreamed of his fetish: for example, he was in a room wearing only a pair of mackintosh trousers and was aware of the clamminess of the garment around him, and stated that the most important part of the lure of a mackintosh garment was its clammy feeling, and for that reason he wore such garments next to the skin. He concluded that "this seems to me that in stimulating myself in this way I am reproducing conditions produced by my mother in infancy."

From the cessation of LSD treatments in March of 1956 he was seen at intervals of two to three weeks and ultimately in May, 1957, he achieved orgasm, two years after treatment was started. Again, his wife's variable attitude delayed progress, but in September, 1957, he reported regular and successful relations over the previous eleven weeks and was thereupon discharged.

At a follow-up interview three months later the patient reported that his wife was three months pregnant and even though she had been in hospital with hyperemesis and he had been living with his own parents, he had not returned to his fetish or the solace of languages.

In summarizing the clinical material obtained from this patient under LSD treatment, it is worthy of note that most of the material produced was relevant and that there was little diversion into the irrelevancies which often delay formal analysis. In contrast to much material elicited in earlier work at this hospital which, as described by Sandison (8) showed a Jungian bias, this case seemed to develop along Freudian lines. Other cases of sexual problems in men treated by the author have proceeded along very similar lines. It should be noted that this case yielded one archetypal experience, as described above.

DISCUSSION

The psychopathology of fetishism remains a subject for considerable discussion. The presented case is interesting in that the patient appeared to show fetishism in a pure form, uncomplicated by homosexuality or transvestism. This would appear to be in agreement with Freud's (4) statement that fetishism is a safeguard against homosexuality, though this is not accepted by Weissman (11) in his recent paper.

Regarding the significance of the fetish object, Wulff (13) describes five cases of fetish objects in childhood and concludes that in infantile fetishism normal development is disturbed by adherence to the first object of the oral component of the sexual instinct, the breast. Winnicott (12), however, criticizes this viewpoint and believes that these are normal transitional objects and a healthy experience.

Hadfield (6) states that he had found the fetishistic object to be a breast substitute in all cases he has analyzed, and Allen (2) supports his view.

There is, however, a large body of analytic opinion, notably including Greenacre (5), Gillespie (4), Payne (7) and Freud (3) himself, which regards fetishism as caused by castration trauma and anxiety. Such were not shown by the patient described here. It seems that there are still grounds for a theoretical discussion of the pathology of fetishism.

In assessing the value of LSD in treating

this patient, an attempt was made to find reports of similar cases in the literature, to compare the length of treatment required before symptoms were overcome. This has proved difficult; for instance, Gillespie (5) described a case treated for nearly three years before interruption of the analysis, in which mackintoshes played a part. He related the mackintosh fetish to much oral, anal and urethral material, but also to the period of milk feeding, the rubber of the mackintosh being a substitute for the rubber teat, "a memorial. . . . to the trauma of weaning."

S. M. Payne (9) also illustrates her paper with an account of a mackintosh fetishist, but does not state the length of treatment. Together with other authors she stresses the importance of the smell and skin sensation of the fetish. These are both well illustrated in the present case, the importance of touch being suggested also in the interpretation of the Rorschach stimulus.

In the absence of reliable data on which to base comparisons, evaluating the effect of LSD becomes highly subjective. The writer has two strong impressions: that the use of the drug led to the emergence of relevant material much earlier than might have been expected without it, and that this effect enabled the therapist, who is not a psychoanalyst, to relieve the patient's symptoms. These are, of course, no more than clinical impressions. A carefully controlled trial of LSD in relation to psychotherapy will be necessary before its value can finally be assessed.

SUMMARY

A case of fetishism treated with psychotherapy assisted by LSD is described. The theories of the development of fetishism are discussed and an attempt is made to evaluate the drug.

REFERENCES

1. Abramson, H. A. Lysergic acid diethylamide III as an adjunct to psychotherapy with elimination of fear and homosexuality. J. Psychol., **39:** 127–155, 1955.
2. Allen, C. *The Sexual Perversions and Abnormalities*, pp. 180, 256–270. Oxford Univ. Press, London, 1949.
3. Freud, S. Fetishism. In *Collected Papers*, Vol. 5, pp. 198–204. Hogarth Press, London, 1950.
4. Gillespie, W. H. A contribution to the study of fetishism. Internat. J. Psycho-Analysis, **21:** 401–415, 1940.
5. Greenacre, P. Certain relationships between fetishism and the faulty development of the body image. Psychoanalytic Study of the Child, **8:** 79–98, 1953.
6. Hadfield, J. A. *Psychology and Mental Health*, pp. 376–377. Allen & Unwin, London, 1950.
7. Payne, S. M. Some observations on the ego development of the fetishist. Internat. J. Psycho-Analysis, **20:** 161–170, 1939.
8. Sandison, R. A. Psychological aspects of LSD treatment of the neuroses. J. Ment. Sc., **100:** 508–515, 1954.
9. Sandison, R. A., Spencer, A. M. and Whitelaw, J. D. A. The therapeutic value of lysergic acid diethylamide in mental illness. J. Ment. Sc., **100:** 491–507, 1954.
10. Sandison, R. A. and Whitelaw, J. D. A. Further studies in the therapeutic value of lysergic acid diethylamide in mental illness. J. Ment. Sc., **103:** 332–343, 1957.
11. Weissman, P. Some aspects of sexual activity in a fetishist. Psychoanalyt. Quart., **26:** 494–507, 1957.
12. Winnicott, D. W. Transitional objects and transitional phenomena. Internat. J. Psycho-Analysis, **34:** 89–93, 1953.
13. Wulff, M. Fetishism and object choice in early childhood. Psychoanalyt. Quart., **15:** 450–471, 1946.

BRIEF COMMUNICATION

SOME EXPLANATIONS FOR "UNEXPLAINED MENTAL PHENOMENA REGARDING SUICIDE"

KENNETH R. WURTZ, PH.D.[1]

Some time ago, Greenbank, in an article in JNMD entitled "Unexplained mental phenomena regarding suicide," attempted to explain two unusual events which he had observed.[2] He implied that it was impossible to explain these occurrences without resorting to extra-sensory communication between the people involved. Alternative explanations of a mechanical nature will be offered for the "strange psychic phenomena" of Greenbank's two cases. If there are a number of different ways to explain an event, then explanations involving "extra-sensory perception" should not be accepted, or even proposed, until all rational explanations have been proven untenable. One does not accept a supernatural explanation when a natural explanation is available.

FIRST CASE

Case Summary: A resident who had been behaving strangely was interviewed and diagnosed as an acute paranoid schizophrenia. That night, he wrote a suicide note in Japanese and stabbed himself to death. His roommate simultaneously dreamed of a chicken with its head cut off spurting blood. In the morning, the interviewer, while walking down the hall, saw a red Coca Cola machine and thought, "What if I should find the resident in a pool of blood?" Greenbank concludes, "Thus two doctors were aware, unconsciously, of the exact method that was to be used in the suicide (bleeding to death)." However, no attempt was made to analyze the dream or to determine the unconscious meaning it had for the roommate. Consequently, we cannot conclude that it is related to the suicide since more conventional psychiatric explanations have not been investigated. The only actual similarity would appear to be that blood is involved in both the dream and the suicide. The frequency of dreams involving blood must, of course, be known in order to estimate the chance expectancy of these events occurring simultaneously. And it is reasonable to expect surgical residents to dream about blood rather frequently.

Another example of such "extra-sensory" dreams may serve to clarify the statistical issues. During World War II, a number of dreams, invariably following the same pattern, were publicized. In a typical report Mrs. X dreamed that her son was killed in action and told her husband; then they received a telegram that their son was dead. Certain statistical data are needed before such stories can be properly interpreted. How many times had Mrs. X dreamed this before (when it wasn't true)? How many other mothers with sons in service had the same dream on the same night? Without data of this kind it is not scientifically appropriate to propose any relationship between the two events. To return to the case at hand: How would the roommate's dream have been treated if the resident had not committed suicide that night? Under these conditions, the interviewer would probably have been expected to investigate the roommate in order to analyze and to understand the dream. One might reasonably ask why this was not done.

[1] Department of Psychology, Michigan State University, East Lansing, Michigan.

[2] GREENBANK, R. K. Unexplained mental phenomena regarding suicide. J. Nerv. & Ment. Dis., **125**: 131–132, 1957.

There is some reason to believe that the interviewer actually made a prediction of the suicide. Would suicide be a reasonable prediction considering what was known about the resident? The facts that were available do not appear to be inconsistent with a prediction of a suicide attempt. The diagnosis of paranoid schizophrenic suggests that the resident told the interviewer about the "profane and derogatory comments" concerning himself that he "heard" over the paging system of the hospital. It is highly likely that the resident indicated that he felt he was a disgrace and had lost honor. The resident, a Japanese, had in effect lost face. It is submitted that these circumstances alone would suggest the possibility of suicide, and that the instrument used would be a knife.

SECOND CASE

Case Summary: A female patient made several suicidal threats to her therapist and then slashed her wrists with a razor. There was a history of suicide in her family; moreover, the patient had seen a woman commit suicide. Immediately preceding the suicidal attempt a number of severely traumatic events were experienced by the patient. Her best friend was an art student who had not seen the patient for two weeks previous to the suicide attempt. At 7 o'clock one night the art student had the "strangest feeling" and drew a picture showing a human hand with the wrists cut and blood running from it. When the patient returned home the artist called her and asked, "What happened at seven tonight?" The suicidal attempt had in fact taken place at 7:20 that same night. Greenbank implies that these events could not have taken place without some form of extra-sensory communication between these two individuals.

There are at least three possible explanations of these events, none of which involve postulating anything remotely resembling extra-sensory perception. One possibility is simply that of a coincidence. A second is that the artist predicted the suicidal attempt on the basis of her knowledge of the patient. A third alternative is that the therapist was hoaxed by the patient and the artist for some reason unknown. On the basis of the information Greenbank supplies there is no reason to reject any of these alternatives.

The first alternative postulates no relationship between the two events, and again certain statistical data would appear to be needed in order to estimate the chance expectancy of the occurrence of the events. How many suicidal attempts is Greenbank familiar with where no unusual events occurred which necessitated the introduction of his hypotheses? Is this one case an unusual coincidence enough to reject a simple chance nature of the simultaneous occurrence of these two events? A careful appraisal of the art student is clearly indicated. The artist reported that she drew the picture on impulse, for no reason at all; is this statement to be accepted without qualification? The most likely interpretation of such an impulse is that it has unconscious determinants, and this possibility was not investigated.

A second possible explanation is that the artist, because of her knowledge of the patient, was simply predicting the suicidal attempt. The remarkable timing of the artist's prediction may simply show that she is an accurate predictor of her friend's behavior. It would not be unreasonable to investigate the artist in the attempt to determine what cues—at a conscious level or otherwise—she used in making her prediction.

The artist was undoubtedly aware of the patient's suicidal threats, of the suicides in the patient's family, and of the recent traumatic events that the patient experienced. In light of this there would be nothing especially mystical about a prediction of suicide. Greenbank feels that it is important that the patient had never threatened suicide by slashing herself and that this means was not utilized by any of the members of her family. Yet it is entirely possible that

the art student had information, of which Greenbank was unaware, that was relevant to her specific prediction. This was apparently not explored. It should also be noted that wrist slashing is not an unusual means of attempting suicide, especially on the part of women. The fact that the artist telephoned the patient would appear to favor this alternative, as it suggests that she was aware her picture represented a prediction about the patient.

Greenbank considers it very important that the artist and the patient had not seen one another for two weeks previous to the attempted suicide. He implies that the artist would not have enough recent knowledge of the patient's behavior to predict the suicidal attempt. However, this time interval can also be interpreted as support for a purely mechanical prediction. Consider the following sequence. Two weeks pass and the artist has not heard from her best friend, who has obvious suicidal tendencies. Perhaps the artist feels guilty because she has neglected her friend. She then predicts a suicidal attempt. It is submitted that there would be nothing extraordinary about such a sequence of events, nor the validity of the prediction.

A third alternative is that of a cooperatively contrived hoax. Greenbank rejected this possibility on the apparent grounds that the two girls would stand to gain nothing from it. For the writer, however, there are some possible reasons for a hoax which would seem less far-fetched than an explanation based on extra-sensory communication between the patient and the artist. Thus, the patient might simply have used this as a form of resistance. The patient may have been aware of the therapist's readiness to accept "psychic phenomena," and so contrived the hoax with her friend to deflect the therapist from an exploration of threatening personal problems.

In summary, there seems to be no reason to invoke extra-sensory communication to explain the events in these and similarly reported cases.

BRIEF COMMUNICATION

THE GLYOXYLIC ACID TEST FOR SCHIZOPHRENIA: OBSERVATIONS IN TWO HOSPITALS

T. D. LOVEGROVE, M.D.,[1] J. B. DERRICK, PH.D.,[2] C. W. BUCK, M.D.[3] AND G. E. HOBBS, M.D., F.R.C.P.[3]

Many metabolic abnormalities have been reported in schizophrenia. One of particular interest has been Riegelhaupt's study of the urinary glyoxylic acid reaction, in which a highly significant difference was observed between schizophrenic subjects and both non-schizophrenic psychotic and normal subjects (3). The possibility that this reaction might provide a simple specific test for schizophrenia calls for further investigation regardless of the more profound metabolic implications. Presented here is a report of experience with the glyoxylic acid reaction among subjects in two mental hospitals in the London area, the Ontario Hospital and the Psychiatric Division of Westminster Hospital for Veterans.

METHODS

Three groups of subjects were studied at each hospital: normal subjects (members of the nursing and attendant staffs), schizophrenic patients and non-schizophrenic psychotic patients. At the Ontario Hospital, subjects of both sexes were studied, but at Westminster Hospital, all subjects were male.

The first morning urine was tested within a few hours after voiding, using the method described by Riegelhaupt (1). Since the urine specimens were identified only by code numbers each test was read without knowing to which group the subjects belonged. At Westminster Hospital the test results for patients receiving daily doses of 50 mg. or more of phenothiazine drugs were treated separately in the statistical analysis. The urines of most of these patients were checked for phenothiazine by the method of Forrest (2).

RESULTS

Table 1 compares the results reported by Riegelhaupt with those of the present study.

Psychotic Subjects. Comparable proportions of positive reactions were found among schizophrenic and non-schizophrenic patients in the Ontario Hospital series and in each of the two Westminster Hospital series.

Significantly higher proportions of positive reactions were found among patients receiving phenothiazine drugs regardless of their psychiatric diagnosis. That this result represented a specific effect of phenothiazine and not some clinical difference between patients receiving and not receiving this medication was shown in the following way. When patients not receiving phenothiazine at the time of the first test were given the drug for ten days and re-tested, the proportion of positive reactions among them was raised. Conversely, when patients receiving phenothiazine at the time of the first test were retested ten days after discontinuing the drug, the proportion of positive reactions was lowered.

[1] Westminster Hospital, Department of Veterans Affairs and Department of Pharmacology, University of Western Ontario, London, Ontario.

[2] Westminster Hospital, Department of Veterans Affairs and Department of Biochemisty, University of Western Ontario, London, Ontario.

[3] Departments of Preventive Medicine and Psychiatry, University of Western Ontario, London, Ontario. The writers acknowledge with gratitude the cooperation given by the Superintendent, Dr. A. Mc Causland and Assistant Superintendent, Dr. D. M. Wickware, of the Ontario Hospital, London, Ontario, and the Superintendent, Dr. E. A. Fergusson, of Westminster Hospital, London, Ontario, in providing subjects and facilities for tests, and the technical assistance of Miss E. B. Rankin.

TABLE I

A Comparison of the Results of the Glyoxylic Acid Reaction Reported by Riegelhaupt with those of the Present Study

	Normals		Schizophrenics		Other Psychotics	
	N*	Positive %	N*	Positive %	N*	Positive %
Riegelhaupt	12	0	65	78%	55	15%
Ontario Hospital London (not on phenothiazines)	49	6%	60	30%	50	38%
Westminster Hospital (not on Phenothiazines)	51	25%	73	26%	22	32%
Westminster Hospital (on phenothiazines)			76	90%	10	90%

* Total number of tests.

Further statistical analysis of the Westminster Hospital test results, not shown in Table 1, revealed no significant differences among the diagnostic sub-groups of schizophrenia.

Controls. The Westminster Hospital normal subjects showed a significantly higher proportion of positive reactions than normal subjects in either the Ontario Hospital or the Riegelhaupt series. To examine further this discrepancy, a second series of specimens from normal subjects at the Ontario Hospital was tested at the Westminster Hospital laboratory and read independently by two individuals who had performed the original tests at each hospital. The discrepancy was explained to our satisfaction by the tendency of one reader to call weakly positive what the other considered negative. This observation, taken with the close agreement between the results for the psychotic series at the two hospitals, suggests that normal and psychotic subjects may differ quantitatively in the relative frequency of weakly and strongly positive reactions.

CONCLUSION

The results obtained provided no evidence that the glyoxylic acid test is specific for schizophrenia. These results do, however, confirm Fleischhacker's suggestion (1) that such drugs as chlorpromazine have an influence upon the glyoxylic acid reaction. It may well be that the high proportion of positive reactions observed by Riegelhaupt among schizophrenics is related to phenothiazine medication.

REFERENCES

1. Fleischhacker, H. H. and Lancaster, J. B. Studies on schizophrenia, IV: The "glyoxylic acid" reaction on the urines of schizophrenic and other phychoses. J. Nerv. & Ment. Dis., **127:** 462–465, 1958.
2. Forrest, F. M., Forrest, I. S. and Mason, A. S. A rapid urinary test for chlorpromazine and pacatal: a supplementary report. Am. J. Psychiat., **114:** 931–932, 1958.
3. Riegelhaupt, L. M. Investigations on the glyoxylic acid reactions on urines from schizophrenic and other psychotic patients. J. Nerv. & Ment. Dis., **123:** 383–385, 1956.

BOOK REVIEWS

FISCHGOLD, H. AND MATHIS, P. *Obnubilations, Comas et Stupeurs: Etudes Electroencephalographiques.* Masson & Cie, Paris, 1959. 124 pp., illus. 3.000 fr.

This monograph is based on extensive clinical and electroencephalographic studies of 145 patients suffering from disturbances of consciousness of varying degrees. The contents include descriptions of the methods of examination, electroencephalographic signs of the comatose stages, the stages of coma, and a discussion of the development of the comatose states.

After the first chapter in which the material is given, Chapter II describes the methods. The neurological, and as far as possible, the psychological examinations are extensive. The authors are especially interested in the ocular signs. They stress in particular the importance of judging the effect of sensory stimuli on the patient's behavior and on the EEG.

The EEGs are taken with various types of apparatus, using up to 22 channels. As we have learned to expect from this center several other variables are recorded simultaneously with the EEG, for example: respiration, the electrocardiogram and eye movements.

In the beginning of Chapter III the authors make the important statement that they know no specific electrical morphology of the comatose stages, although the majority of waves encountered have frequencies below the alpha band of 8–12 c/sec. The most important EEG signs for assessing the comatose states are, however, not the frequencies but the reactivity of the EEG and the topography of the abnormal waves.

In Chapter IV studies of the clinical and EEG signs during the various stages of coma are described in detail. The authors conclude that by using all available data it is possible to distinguish between sleep and comatose states and, moreover, to distinguish the various stages of coma. Briefly summarized the stages are as follows:

Stage 1: Clouding of consciousness. The patient is hypersomnic, but can be awakened. The responses of the patient are slow and confused. No serious impairment of autonomic reflexes is apparent. The EEG is variable, usually with slowing and flattening of alpha rhythms, diffuse theta activity and occurrence of monomorphic delta paroxysms in the frontal areas. Reactivity is not only conserved, but is enhanced over that of the waking state.

Stage 2: Pure coma. The patient does not reply to questions. Peripheral stimulation causes only some motor agitation or monosyllabic grunts. The eyelid reflex to threat begins to disappear, but the coughing reflex is still preserved. The EEG shows flattening but pin prick on the hand causes recurrence of rhythmic monomorphic waves in the frontal areas. Reactivity, however, is much reduced from that in the previous stage.

Stage 3: Complete coma. All contact with the patient is lost. The ocular reflexes have disappeared. Often there are signs of decerebrate rigidity. There are vegetative and respiratory difficulties. The EEG is monotonous with much slow activity and almost no reaction to stimuli.

Stage 4: Acute cardio-respiratory arrest. The patient can be kept alive only by reanimation of the heart, by artificial respiration and by injection of hypertensive drugs. The EEG shows complete electrical silence, usually irreversible.

At the end of this chapter, the value of these data for the prognosis is assessed.

In Chapter V the development from one stage to another is described. In addition there is a discussion of the relation of comatose states to mutism and to psychomotor regression in the child.

The book is richly illustrated by 54 fig-

ures, including both EEG and polygraph recordings and photographs of the patients. The bibliography is exhaustive and contains 84 references, but unfortunately there is no index.

In the opinion of this reviewer the authors have made great progress in creating some order in the chaos of ideas and nomenclatures relating to the various stages of coma. Their scheme may not meet with universal approval, particularly as the terminology is inadequate, and is used, as they themselves acknowledge, "for lack of a better one." Nevertheless the book undoubtedly will be of great value to all concerned with this subject and is essential reading for all electroencephalographers who have to deal with patients of this kind.

W. Storm van Leeuwen

BOK, CURTIS. *Star Wormwood.* Alfred E. Knopf, New York, 1959. 228 pp. $3.95

Star Wormwood depicts in three sections the background and early development of a teen-age boy, his crime, his trial and execution, and to each section is appended a comment based upon three William H. White lectures delivered by the author at the University of Virginia Law School, in April of 1957. Curtis Bok has had a distinguished career as lawyer, author and jurist. He had been both a prosecutor and a Voluntary Defender, has had 21 years on the trial bench and since 1958 has been a Justice of the Supreme Court of Pennsylvania.

The story of *Star Wormwood* is fictional; the comments are a protest against a criminal and penal system founded on vengeance. The object of this vengeance is Roger Haike, a symbol for an uncounted number of individuals in our society whose beginnings leave upon them a mark of emptiness in human values. Within a few pages Roger reaches 17, he is set adrift, his father dies when he is small, his mother leaves him to a relative who, in turn, abandons him in death. His physical existence is parlous and his emotional life is barren of human exchange. From the narrative we see little of his under side, save for his own terror when once he had a glimpse of the bottom of a deep pool; a glimpse of the depth within himself out of which some deed might emerge. Beyond this hint of the latency of impulse, from the story we can sense only vaguely the antecedent conflicts within this boy which would find eventual expression in a killing.

The reader is carried through the crime of murder and cannibalism. Roger finds himself confronted by Angela, the 13 year old sister of his friend, Joe. At this moment Roger enters innocently into a web of circumstance of incest and consequent pregnancy. Angela's resentment against her seduced brother spills over onto Roger as she intercepts his forbidden business of roasting a rabbit in the furnace which he tends in a local school. Angela threatens to expose Roger. In panic, he restrains her and in the excess of his impulse strangles her and afterwards bungles an attempt to dispose of her body in the furnace. A part of Angela substitutes for the first object of Roger's need and intention to meet hunger. Something came out of the depth of Roger and when it was done he stood as uncomprehending of it as before.

The first section depicting the crime moves quickly and fixes the reader's interest. However, one finds the story wanting in those elements of causal sequence which give to Roger's deeds a psychological thrust and meaning. The story does not quite develop a dynamic set for either the killing or the eating of a part of the victim. She was not previously linked to Roger's life. Earlier female images merely passed out of his life—they did not threaten him. The oral link between Roger's so-called cannibalism and the past comes to us only in the revived memory in his father's playful reference to eating him and in Roger's childlike logic that the father could not eat him because "a part would stick out."

There remains only the common-sense explanation that Roger willfully killed to silence one whom he had ravished and that he ate a part of his victim to allay hunger. One may concede that the author's fictional piece need not have psychological consistency, if it serves the purpose of setting the stage for what is to come closer to real life in the trial and execution. In these, there is less of Roger and more of the irrationality of mass response to the crime carried within the forms and logic of our criminal law. Again, it may be remarked that the forced use of cannibalism, which adds both a bizarre and repellent note, tends to distract from the author's principal theme of community response of vengeance to commonplace homicide. Roger was made to break an unwritten taboo more archaic and visceral than either incest or man slaying. It placed him beyond reach of his fellow creatures in the jury box. In including the issue of cannibalism, the author precluded any natural sympathy for the accused and introduced a distraction beyond the needs of his main thesis. A case taken from real life would have transcended a literary statement to bring to it an emotional acceptance and the reader's identification with real life people and events.

Roger was discovered and indicted for first degree murder and brought to trial. It was a foregone conclusion that Roger would be executed and there was a visible anticipatory excitement in those who would try him. The machinery of justice provided the theater for the working through of the tribal response to a broken taboo, a process by which in vengeance the community undid Roger's crime by duplicating it.

This reviewer was troubled by the author's comment, "The dreadful truth is that there are more innocent people convicted than there are guilty people acquitted. There is no doubt of this when we include people who are guilty of something but are convicted of something else and when the forfeit is life or liberty, they have a right not to appreciate poetic justice." Is this really true and is it statistically provable? Justice Bok's "dreadful truth" is that our system of justice convicts more innocent people than it acquits guilty people. The number of convicted innocents is always too large, but the number is small when we consider the vast number of persons tried. Does the "something else" refer to the way of law by which it convicts a racketeer of income tax evasion in order to punish him for his racketeering? We can join his protest against the imperfection of justice, but the imperfection is not as clearly disclosed in his statement as it is when he speaks less of the abstraction called justice and more of the priestly-minded people who dispense it. Justice Bok's comments cover the questions of "truth" and "fact" as they are talked about in law courts. He says, "No longer can these different things stand revealed but not explained," and he envisions a new climate of opinion as to what is truth and fact forced by the influence of psychiatry when we will no longer revere the law as a thing of beauty for its certainty.

The section on the trial is a moving picture of a court drama on two levels, one the thrust and parry of a game between the prosecution and the defense with the judge in the middle; the other, in the confusion of the languages of law and psychiatry. Roger's defense is temporary insanity. Justice Bok takes the reader through the defense of insanity as determined by the M'Naghten Rule of knowledge of right and wrong, which places the opposing psychiatrists in the position of experts on a moral issue rather than of reporters of medical information. There was no "battle of experts" here; merely a testimony on one side diametrically opposed to that of the other which in effect reduced the medical offerings to double talk and the jury to no comprehension of the meaning of Roger's crime.

Justice Bok calls the criminal law the black sheep of the legal family, unattractive to the average lawyer. He writes, "It has remained medieval with minimum damage to

the populace. There is little law in it. There are the definitions of the crimes, a few aphorisms about trial procedure and evidence and sentencing, and the great monuments of civil liberty, like the right to trial by jury, to confrontation by one's accusers, to the benefit of a reasonable doubt, and to due process. Murder, robbery, assault, rape and fraud have been quite well understood since the days of Julius Ceasar." He asks, why, if the criminal law is so simple and static, the difficulty in achieving uniform results? He answers, the growth of the welfare state and the growth of psychiatry. With the advent of psychiatry and companion behavioral science, "... it is also growing clear that the importance and effect of free will are becoming less and less as a person's early influences and motivations are revealed." Justice Bok accepts the demonstrations of psychiatry that show the underside of the mind and how it may determine a behavior contrary to common sense, how in the unlawful deed there may be a deeper motivation, a primary gain, which achieves a gratification of its own. Otherwise, how does one explain senseless antisocial acts? Here criminal law meets with difficulty when it tries to assess the responsibility of a criminal for his crime. Justice Bok attempts to dissect this difficulty. He says, "The law presumes men sane, psychiatry presumes them mad. Both are furious because it seems impossible to draw a line between harmless and harmful madness. The psychiatrists know that the line can be drawn but they know not where. The lawyers know where to draw it but they know not how. They talk on different levels." This style of discourse is imprecise. That psychiatry presumes men mad is a piece of folklore believed by many lawyers and some judges. The mad man is a social-legal concept, a creature of expedience, outside of the conceptual operations of psychiatry. In psychiatry the mad man exists only as a description of behavior which the law chooses to call mad.

Justice Bok offers a novel comment on the M'Naghten Rule. He believes that M'Naghten is more than a rule; it is a philosophy which supports the belief that if it is *wrong* to rob, it is *right to* punish the offended. This dichotomy "expressed in M'Naghten is not the true cause and effect but seems to be, and hence it keeps our legal process punitive, the keystone of a vengeful penal system." Of interest to psychiatrists is his statement that psychiatry is not necessary for the determination of insanity. This view is correct. Insanity is a legal concept and exists only in the sense that the law defines and determines it. It may be determined by legal standards of the moment which may or may not have relevance to concepts of mental illness as understood by the medical profession. Justic Bok states that as the place for M'Naghten continues to be narrowed, it will eventually expire supplanted by a legal psychiatric emphasis on treatment. With M'Naghten will go the notions of *mens rea*, the guilty mind and eventually the adversary method of trial. The only need for psychiatry at trial will be to determine whether the accused is "too insane to plan his defense and the measure of insanity will not be the M'Naghten Rule but the psychiatric rule."

Justice Bok outlines the new penology. He recognizes that the distribution of term punishment governed by a code may satisfy the mass conscience but it does not realistically meet the needs of the individual offender. He speaks with insight when he says that, on the one hand the man who murders may be so purged by remorse that his is not a menace to society and need not be "brought to trial at all." On the other hand, there are some who after adequate study may be regarded as untreatable and expendable "monunments to our lack of wisdom." Justice Bok does not favor the indeterminate sentence but one which would include a short and flexible minimum, a long maximum and an intermediate period fixed by a diagnostic or a parole board of psychiatric, medical and sociological procedures of an increasing educative value. Many will welcome his recom-

mendation that the criminal trial cease to be an adversary spectacle and instead become an impartial inquiry no longer hagridden by the M'Naghten Rule; also that the proper place of psychiatry not be in the court but in the prisons. However, others may advance the view that psychiatry does have a limited place in the trial.

In the trial, lawyers and doctors are at cross purposes and when is added the public attitude we can expect confusion. Justice Bok offers a way out of this confusion. He would keep the psychiatrist out of the courtroom and leave to the court its primary function of finding facts. The only place for psychiatry is in penology, following conviction. Should psychiatry have a place in public view? Would he consider that out of public view and under conditions which exist in American penal institutions only exceptionally can psychiatry operate as a self-determining scientific discipline, not as a dependent creature of a bureaucratic machine. Worse, in this setting of mass manipulation psychiatry can become a tyranny in the name of science. Justice Bok passes these possibilities. At the same time he isolates lawyers and judges from the influence of psychiatry in the courtroom. Psychiatry in the courtroom, limited to the submission of psychiatric facts as understood and described in terms acceptable to psychiatry, should supply such information that could have an "increasingly educative value" to the community, a value which Justice Bok recognizes. The courtroom should be a public classroom. Without this "education" the law is not likely to advance beyond the anachronisms Justic Bok himself condemns. The late President Lowell of Harvard University said that the test of democracy is in its ability to use experts. Justice Bok's view would have wider support if he proposed a reform of jurisprudence which would eliminate a kind of psychiatry from the courtroom now imposed by the law.

In the section on the execution, the author is at his best in a compelling description of the prison, the killing of Roger and in the development of his protest against capital punishment. His evidence against it is conclusive. But his comments on the causes of crime and delinquency are hortatory and inconclusive. Thus, he gives first place among causes the failure of the police and courts to solve, by capture and conviction, more than one crime in five. Is the failure to catch and convict wrongdoers a cause of crime? The second cause is liquor. Is it not possible that liquor prevents as many crimes (even if not more) than it causes? Third on the list is broken, severe, neglectful and unsympathetic homes. Again, are not the overindulgent and non-directional homes also causative? Fourth, "... poverty and the mass media like the motion picture, television and publications that offer shows of crime and violence." Are there statistical data available which show that crime is caused by such mass media which supply the population with an undiminishing fare of crime in fantasy? Without such crude substitutions in fantasy, would we have more crime in fact? In the fifth order are placed need of money for food, doctors, rent and the like. Those who have had firsthand experience with criminals note that a lack of money is readily offered as a causative motive for theft, but rarely is it the real cause. Mark Twain commented that, "A crowded police court docket is the surest of all signs that trade is brisk and money plenty."

Much has been declaimed on the question of crime causation and much of this still remains popular myth. Justice Bok is on safer ground when he attacks our penal system as a cause of crime. The crime of punishment is the crime of the law abiding against the scapegoats of society. He deplores the plight of the juvenile in our industrial society. "Society, however, allows a seven year gap between the crucial ages of 18 and 25," in which idleness is the corrupter of character and in the author's view this interval is a period of acquiring an education in crime. Here he makes a challenging assertion, "Peo-

ple are born good but must learn evil." This will be disturbing to moralists who believe that growing up is a process of renouncing self-centered (evil) ways for order to attain goodness. It will also be disturbing to psychiatrists who find that people are born neither good nor evil. There is no magic in the 25th year of life. Here the author has found that first offenses tend to drop in frequency after 25 and correlates this with the findings of psychologists that mental capacities reach their fullness at this age. He believes that we neglect our young by not keeping them occupied and he notes that relatively few college-educated people commit crime. The age span between 18 and 25 is a critical period insofar as in it occur the largest number of failures of social adaptation manifest in all forms of mental illness and in crime or in behavior partaking of both. And from a mass of evidence it is clear that both mental and criminal adaptive failures are set in the earlier tender years and not learned in the 18 to 25 period. Justice Bok says that until one becomes 25, "... he can and should be considered a potential killer, raper and thief, if he has as little as five minutes in which to grow bored and make the wrong choice. After 25 society can safely take a chance on him." Here the author is speaking lyrically of the statistical frequency of crime by age grouping, but it would be interesting to test this thesis that merely keeping young people busy or sending them to college would meet the problem. Antisocial patterns are seeded early and they tend to bloom in adolescence. It would require more than mere occupation to meet the problem; it would require much psychological work as well, applied to both the young person and his educators.

Justice Bok refers to George Bernard Shaw's argument that we are perversely sentimental about the offenders we choose of murder legally. We may kill only the sane. If we permit the death penalty at all, we should execute the insane killers, not in vengeance or in bad blood, but dispassionately, painlessly, even apologetically. For the sane killers we should give a different consideration, for most of them will not repeat their crime, "... for a man does not realize what a fearful thing it is to murder until he has done it. The average murderer is far less a continuing social menace than the professional thief." Some readers may ponder whether Justice Bok speaks for himself or merely cites Shaw as an advocate of capital punishment for insane killers. Later he makes his stand clear that when we kill incurable mad men we are reacting to fear and hatred, and he joins in Wertham's statement that, "To execute a sick man is burning witches."

Justice Bok knows that the legal concept of insanity is mischievous in the view of modern social science, which regards insanity merely as an alteration of personal legal status, assigned to one by legal authority, arbitrarily sanctioned by circumstances of time and place. Justice Bok writes that psychiatry presumes all men mad and in an Erehwonian sense this is conceded. In every man can be uncovered a madness at some time, under some conditions and in some measure, and it is the imputation of *Star Wormwood* that our vengeful criminal law is every man's expression of a kind of madness—what Justice Bok calls "mankind's moderate average madness."

Justice Bok writes of three developments in penology: 1) the larger use of administrative bodies in sharing sentencing judgment with the courts; 2) the trend toward a wider range of penal institutions in each state, from the fortress type to the minimum security and open farm or forestry camp, and 3) the larger use of vocational training and education in preparing prisoners for release. The author gives a description of the modern penal institution at Chino, California, a creature of political accident, which has succeeded beyond the expectation of its founders. Like its counterparts in the Federal prison system at Seagoville, Texas, Ashwell in England and the van der Hoeven Clinic in Holland, Chino has made a full demon-

stration that we no longer need a penology based upon fear and barbaric repression. The new penology envisions the use of available knowledge to make the punishment fit the offender and not the crime, and in this scheme it is possible that even some murderers may not be imprisoned at all, and prisons may be more like special colleges and vocational schools than jails, where through the prescriptions of the law the process will go beyond the point of rendering an offender harmless and incapacitated to make him useful.

Justice Bok cites three cases illustrative of the failure of society to handle crime intelligently; first, the failure of the law as related in his fictional case of Roger Haike, a second, a real life case of two young boys whose impulsivity brought into its train the death of two persons. Both pled no defense. For some 15 months prior to trial one had been held and observed under virtual custodial restraint in one of the leading psychiatric institutions in America, had been found to have a disabling mental illness with possible neurological complications. There was no trial of the issues of fact of the crime; only the hearing of medical reports and the conclusions drawn from them. The defendant was regarded as having a psychiatric disability for which there could be no logical choice other than indeterminate treatment which would be possible only under probationary auspices. It was concluded that since no such treatment was available in prison, a sentence to a prison would merely postpone it, and risk the loss of what gains had been already achieved. Justice Bok writes that this case was "smothered in psychiatry, which is for the pure in heart who have been overburdened and genuinely distressed, not for those that use it as a device for getting out of a tight corner ... Prison was, of course, the place where they had to go." The court sentenced the defendant to two to six years to a state penitentiary. Two weeks later the court reduced the sentence to one and a half to three years and the defendant was removed from the state penitentiary, which had at least a token rehabilitation staff, to a county jail where no psychiatric treatment facilities existed. One year later the Governor commuted the sentence. It is difficult to concede the failure of psychiatry in this case. The reader is given to accept that psychiatry was used to defeat the ends of justice with its relative imprisonment, that the best of psychiatry was submitted to get one of impure heart and not overburdened or genuinely distressed out of a tight corner. We do not learn from the author the aftermath of this case. The court acted against the judgment of psychiatry; the boy was jailed. Has subsequent observation vindicated this decision? Thus what Justice Bok says in theory one ought to do in practice the court does not do. It is his defense of this inconsistency that mars an otherwise excellent and highly persuasive commentary on mid-20th century criminal jurisprudence.

The third case of Albert Fish relates the failure of law, of psychiatry and of humanity. Fish, a chronic schizophrenic, had molested at least 100 children and murdered some 15 of them. Some he cooked and ate. At least eight times the law had failed to recognize his mental disease at the time of prior arrests. At his trial the psychiatric testimony made little sense. Fish passed M'Naghten because he knew what he was doing and that it was wrong to do it as anyone, even a schizophrenic, can know. Fish was executed.

Star Wormwood is an important contribution to the literature of legal reform, offered by one eminently qualified to criticize our legal institutions. It will be an influential contribution because it comes from the side of law. Its balance would have been more fully reached if Justice Bok had spelled out both substantive and procedural implementations to his argument against retaliative punishment. For example, how would he consider the larger use of collegiality whereby all major criminal cases are tried *en banc*, or perhaps the procedure adopted in the Italian

Juvenile Court Act of 1934 (Article 2) whereby one of three judges is a citizen distinguished in social welfare, experienced either in biology, in psychiatry, or in criminal anthropology? Justice Bok makes no mention of the need for social science training of law students or for career non-political incentives for judges. *Star Wormwood* is recommended reading for all who are concerned for the ultimate directions of our criminal law.

Philip Q. Roche

STERN, ERICH. *Die Psychotherapie in der Gegenwart.* Rascher-Verlag, Zurich and Stuttgart, 1958. 474 pp., Swiss/francs 33.

The term psychotherapy threatens to become a stereotype for all psychological treatment methods short of formal psychoanalysis as practiced in this country. Thus any comprehensive treatise on psychotherapy will meet with curiosity by medical as well as paramedical practitioners.

The second volume of Erich Stern's "Handbook of Clinical Psychology" is devoted to a broad review of present day psychotherapy. The editor and fifteen contributors—all representative European and American investigators and therapists—indicate by the subtitle their purpose to assess "directions, tasks, problems and applications" of this field. They discuss psychotherapy not merely from a clinical point of view, but follow its historical development from a therapeutic method into those conceptualizations which now markedly influence our medical and social culture.

So ambitious a scope has been realized to a surprising degree. The writers give evidence of their broad familiarity with practice, concepts and literature on both sides of the Atlantic, a viewpoint too often lacking in our own publications. In each chapter, undisputed facts, methods and methodology, questions of interpretation and elaborations of theories are re-evaluated without loss of clarity or overall perspective. A concluding chapter summarizes and correlates the contributors' material, highlighting common denominators as well as divergencies. The absence of polemics, modesty of claims, and skeptical attitude toward prevailing dogmatisms characterize the book and justify Stern's quotation of Virchow, "that nothing prevents the progress of science as greatly as systems and authorities." An English translation of the book would be welcome.

Klaus W. Berblinger

GORDON, H. L., ED. *The New Chemotherapy in Mental Illness.* Philosophical Library, New York, 1958. xvii + 761 pp. $12.00.

This enormous volume presents a series of short papers and discussions presumably attempting to summarize current clinical experience and knowledge of the tranquilizing or ataractic drugs. It is divided into four groups of papers dealing with:

(1). General Surveys,

(2). Clinical Psychiatric Experience,

(3). Clinical Experience in so-called Related Conditions (which are for some not quite clear reason excluded from the psychiatric sphere), and

(4) Side Effects.

Although there is a certain amount of useful material here, this seems to be a rather peculiar book. One almost has the feeling that the publishers felt it might be profitable at this time to market a pseudo-encyclopedia which might give many doctors feelings of guilt if it did not appear on their office bookshelves—or, at least, might lull the patients who saw it there into a false sense of security in their doctor's ability to "keep up with the times" and his consequent knowledge of new miracles with which to allay their fears and anxieties.

In other words, the book adds nothing to the numerous previous articles, symposia, etc. which have flooded the literature for the past few years. Its roster of authors certainly includes all the necessary, illustrious

clinical names without which any discussion of Rauwolfia, Phenothiazine, Azacyclanol, Mephenesin, Hydroxyzine and Benactyzine would be incomplete. Nor is it merely a paean in praise of doubtful therapy, since it does not fail to point out questionable and even dangerous effects of these substances. However, nowhere is there any real attempt to analyze or carefully assess and integrate the total picture. The bibliography has been so sadly neglected as to be almost non-existent. The print is so small that it is most uncomfortable to read. Despite a few chapters of interest (which have, perhaps, been presented better elsewhere) one is left with a feeling that this is a sort of "what I believe" digest by 167 doctors, which will be of use only to other physicians in districts so outlying and with such poor income that they have no access whatever to other books or journals.

Robert G. Grenell

INDEX

A

Absent father, 387
Abstraction, studies in: Schizophrenia and orality, 564
Acute intermittent porphyria, psychopathology of, 291
Adaptive significance of the dream, 144
  communication in, 145
  interpretation, 146
  physiological factors, 144
  transitional consciousness, 145
Adey, W. Ross, 417
Adjustment and performance, premorbid, implications of for interpreting heterogeneity in schizophrenia, 450
Adolescents from higher socio-economic groups, anti-social behavior of, 467
Affleck, D. C., 492
Age and time, in torticollis patients, 155
Alcoholics, psychotherapy with, 477
Alexander, Martha, 201
Alliances in family of the schizophrenic, 366
Ambivalent mother, separation from, 388
Aneurysms, ruptured, of supraclinoid portion of internal carotid and middle cerebral arteries, 35
Angiography of cerebrovascular patients, 282
Anti-social behavior of adolescents from higher socio-economic groups, 467
Anxiety and the structural hypothesis and post-Freudian ego psychology, 341
Anxiety reactions, comparative effects of phenaglycodol and meprobamate on, 193
Aphrodisiacs: From Legend to Prescription, 508
Apparent motion discrimination test and triflupromazine, 187
Applications of Information Theory to Psychology, 501
Appraisal of duration of stay in outpatient psychotherapy, An, 492
Arnold, De Vere G., 193
Arteries, middle cerebral and supraclinoid portion of internal carotid, ruptured aneurysms of, 35
Asexualization, 499
Association of psychosis with severe renal glycosuria, 196
Athetosis, congenital bilateral
  associated and mass movements in, 125
  contactual responses of hands, feet and lips, 117
  deficit in voluntary movement in, 123
  general description of motor deficit in, 106
  labyrinthine responses in, 116
  motor deficit in, 105
  relation to infant motor responses, 127
  resistance to passive movement in, 117, 126
  resting posture in, 113
  tonic-neck reflexes in, 114
Attneave, Fred, 501
Autistic stage of schizophrenic development, 432
Automation and technology, intrusion of into families, 387
Autonomic nervous system role in radiation reactions, 519
Availability of hexafluorodiethyl ether by intravenous injection as a convulsant in psychiatric treatment, 92

B

Barron, Kevin D., 35
Basic concepts (in Methodological study of Freudian theory), 11
Becker, H., 306
Becker, Wesley C., 442
Behavior of ward, effect of tranquilizing drugs and rehabilitation activities on, 568
Behaviour and Physique, 310
Bellak, Leopold, 76, 206
Beukenkamp, Cornelius, Jr., 501
Bieber, Irving, 235
Bilateral athetosis, congenital, motor deficit in, 105
Biochemistry
  cyanide encephalopathy produced by intravenous route, 302
  eosinophil counts and salivary Na/K, diurnal variation patterns in psychiatric patients, 69
  lysergic acid, effects on visual discrimination in monkeys, 252
  mescaline metabolism, with note on correlations between metabolism and psychological effects, 177
  porphyria, acute intermittent, psychopathology of, 291
  psychosis, association of with severe renal glycosuria, 196
  serotonin, blood and urinary, and 5-hydroxyindole acetic acid levels in schizophrenics and normal subjects, 62
Birch, Herbert G., 162
Bisexuality, narcissism and the dual instinct theory, 207
Bixley, William, 507
Blackwood, W., 204
Blame, defenses against, in family of the schizophrenic, 366

Blood analysis in correlation of mescaline metabolism and psychological effects, 178
Blood and urinary serotonin and 5-hydroxyindole acetic acid levels in schizophrenics and normal subjects, 62
Blood brain barrier of rat, relationship to I^{131}-labelled triiodothyronine, 530
Body image in torticollis, 152
Body sway test and triflupromazine, 188
Bogoch, Samuel, 196
Boisen, Stekel and others' alternative view of the unconscious, 224
Bok, Curtis, 584
Boskoff, A., 306
Bosselman, Beulah, 101
Bouvry, M., 313
Brain
  cyanide encephalopathy produced by intravenous route, 302
  rat blood brain barrier relationship to I^{131}-labelled triiodothyronine, 530
  thalamus and globus pallidus, depth stimulation and recording in with paralysis agitans patients, 417
Brain-damaged and mongoloid children, formation and extinction of conditioned reflexes in, 162
Brain lesions, lateralized, differential effects of on Trail Making Test, 257
Bremer, Johan, 499
Brody, Eugene B., 88
Buck, C. W., 581

C

Carbon Dioxide Therapy, 2nd ed., 100
Carotid compression tests in cerebrovascular patients, 274
Carotid, internal, supraclinoid portion of, and middle cerebral arteries, ruptured aneurysms of, 35
Carr, C. Jalleff, 306
Case of fetishism treated with lysergic acid diethylamide, 573
Castration complex, female, 235
Castration impulses and fears in adult females, 237
Censure, significance of in schizophrenia, 460
Central nervous system effects of ionizing radiation, review of Soviet research on, 511
Cerebral arteries, middle, and supraclinoid portion of internal carotid, ruptured aneurysms of, 35
Cerebrovascular patients
  angiography of, 282
  carotid compression tests in, 274
  lumbar punctures in, 289
  neurosurgical diagnostic evaluation of, 273
  ophthalmodynamometry in, 276
  ventroculo-encephalography of, 289
Chambers, Jay L., 184
Changing conceptions of the unconscious, 222
Chapman, A. H., 29
Chemical Prevention of Cardiac Necroses, The, 309
Chemotherapy
  chlorpromazine, influence of on pathologic emotions and sexual unrest, 171
  hexafluorodiethyl ether, availability of by intravenous injection as a convulsant in psychiatric treatment, 92
  hexafluorodiethyl ether (Indoklon®) and electroconvulsive therapy, comparative study of, 95
  lysergic acid effects on visual discrimination in monkeys, 252
  lysergic acid diethylamide, case of fetishism treated with, 573
  meprobamate, phenaglycodol and, comparative effects of on anxiety reactions, 193
  metrazol convulsive therapy modified by succinylcholine, 198
  phenaglycodol and meprobamate, comparative effects of on anxiety reactions, 193
  Sernyl, new drug causing symptoms of sensory deprivation, 54
  Serotonin and 5-hydroxyindole acetic acid blood and urinary levels in schizophrenic and normal subjects, 62
  tranquilizing drugs and rehabilitation activities, effect of on ward behavior, 568
  triflupromazine, evaluation of therapeutic use of, 184
Child-bearing function in female castration complex, 235
Children, brain-damaged and mongoloid, formation and extinction of conditioned reflexes in, 162
Chlorpromazine, influence of on pathologic emotions and sexual unrest, 171
Circulating eosinophil counts and salivary Na/K, diurnal variation patterns in psychiatric patients, 69
Cleveland, Sidney E., 150
Clinical and theoretical considerations of homosexual panic, 20
CNS
  functional and morphological alterations in resulting from irradiation, 512
  role in acute radiation syndrome, 517
Cobb, Stanley, 416
Cohen, Bertram D., 486
Communication
  between psychologists and psychiatrists, problem in: Psychological test reporting, 76

in dreams, 145
interdisciplinary, psychological report as a problem in, 86
Comparative effects of phenaglycodol and meprobamate on anxiety reactions, 193
Comparative study of hexafluorodiethyl ether (Indoklon®) and electroconvulsive therapy, 95
Competence of psychotherapists, personality differences between more and less competent as a function of criteria of competence, 375
Complex, female castration, 235
Concept of nemesis in psychoneurosis, 29
Concordance and discordance, factors associated with in schizophrenia in monozygotic twins, 1
Conditioned reflex responses, effects of radiation on, 522
Conditioned reflexes in brain-damaged and mongoiloid children, formation and extinction of, 162
Congenital bilateral athetosis, motor deficit in, 105
Consciousness, transitional, in dreams, 145
Contactual responses of hands, feet and lips in congenital bilateral athetosis, 117
Continuum, the process-reactive, 551
429, 435, 442, 450
Convulsant in psychiatric treatment, availability of hexafluorodiethyl ether by intravenous injection, 92
Convulsive therapy, metrazol, modified by succinylcholine, 198
Correlations between mescaline metabolism and psychological effects, 177
Crandall, Archie, 551
Current Concepts of Positive Mental Health, 504
Cyanide encephalopathy produced by intravenous route, 302

D

David, Edward E., Jr., 203
Decision of psychiatrist to refer a patient for psychological testing, 88
Defense against blame in family of the schizophrenic, 366
Defenses of manic patient
personality, 245
selective, 246
Deficit, motor, in congenital bilateral athetosis, 105
Delinquency
adolescents from higher socio-economic groups, anti-social behavior of, 467
Demb, Howard, 162
Deprivation, sensory, new drug causing symptoms of (Sernyl), 54
Depth stimulation and recording in thalamus and globus pallidus of patients with paralysis agitans, 417
Derrick, J. B., 581
Devault, M., 54
Development and integration, schizophrenic, stages of, 429
Diagnostic
criteria, methodological problems of in schizophrenia, 453
evaluation, neurosurgical, of patient with cerebrovascular disease, 273
psychiatric interview, and test situation, different levels of sampling behavior in, 81
Dichotomous typology, schizophrenia as a, 451
Differences in personality between more and less competent psychotherapists as a function of criteria of competence, 375
Different levels of sampling behavior in diagnostic psychiatric interview and test situation, 81
Different behavior of schizophrenic, 367
Differential effects of lateralized brain lesions on Trail Making Test, 257
Differentiation, integration and, in schizophrenia, 542
Differentiation, perceptual, and two dimensions of schizophrenia, 435
Diller, Leonard, 263
Discordance and concordance, factors associated with in schizophrenia in monozygotic twins, 1
Discriminating or universal: Psychological test reports, 83
Diurnal variation patterns of circulating eosinophil counts and salivary Na/K in psychiatric patients, 69
Dot judgment test and triflupromazine, 188
Discrimination, visual
effects of lysergic acid on in monkeys, 252
in schizophrenia, 455
Disturbances in feelings of integrity and well-being in female castration complex, 236
Dobie, Shirley I., 486
Dream, adaptive significance of, 144
Dream interpretation, 146
Dreams and images, influence of subliminal visual stimulation on, 315
Dreams in Folklore, 412
Drellich, Marvin G., 235
Drug, new (Sernyl) causing symptoms of sensory deprivation, 54
Drugs, tranquilizing, and rehabilitation activities, effect of on ward behavior, 568
Dual instinct theory, narcissism, bisexuality and, 207
Duration of stay in outpatient psychotherapy, an appraisal of, 492
Dynamics, personality, in torticollis, 150

E

Ecology, psychiatric, 385
Economics of Mental Illness, 312
EEG
  cerebrovascular patients, neurosurgical diagnostic evaluation of, 273, 280
  paralysis agitans patients, depth stimulation and recording in thalamus and globus pallidus of, 417
Effect of tranquilizing drugs and rehabilitation activities on ward behavior, 568
Effects, comparative, of phenaglycodol and meprobamate on anxiety reactions, 193
Effects, differential, of lateralized brain lesions on Trail Making Test, 257
Effects, hallucinogenic, of brief sensory isolation, 486
Effects of lysergic acid on visual discrimination in monkeys, 252
Ego psychology, post-Freudian, structural hypothesis, problem of anxiety and, 341
Ekdahl, Marilyn, 391
Electroconvulsive therapy and hexafluorodiethyl ether (Indoklon®), comparative study, 95
Electroencephalographic, pharmalogical, and neurological effects of Sernyl (new drug causing symptoms of sensory deprivation), 54
Emotions, pathologic, and sexual unrest, influence of chlorpromazine on, 171
Empathic stage of schizophrenic development, 429
Encephalopathy, cyanide, produced by intravenous route, 302
Eosinophil counts, circulating, and salivary Na/K, diurnal variation patterns of in psychiatric patients, 69
Epilepsy, 505
Erikson, Erik H., 406
Esquibel, Augusto J., 95
Evaluation of therapeutic use of triflupromazine in mental disease, 184
Extinction, formation and, of conditioned reflexes in brain-damaged and mongoloid children, 162

F

Factors associated with concordance and discordance with respect to schizophrenia in monozygotic twins, 1
Family in Psychotherapy, The, 201
Family of the schizophrenic: A model system, 357
  different behavior of the schizophrenic, 367
  family behavior, 359
  function of, 371
  model for differentiating different types of families, 372
  rules in the family, 36
  alliances, leadership, defenses against blame 36
  three-person system in the family, 36
Father, absent, 38
Feelings of integrity and well-being, disturbance in, in female castration complex, 23
Feet, hands and lips, contactual responses of, in congenital bilateral athetosis, 11
Feifel, Herman, 7
Fein, Rashi, 31
Feldman, Sandor S., 30
Feldstein, Aaron, 6
Female castration complex, the, 235
  child-bearing function, 235
  disturbances in feelings of well-being and integrity, 236
  loss of sexual desire and femininity, menstruation function, 236
Female sexuality, 235
  feminine component of, 238
  phallic component of, 239
Females, adult, castration impulses and fears in, 237
Feminine component of female sexuality, 238
Femininity and sexual desire, fears of loss of in female castration complex, 236
Fetishism, case of, treated with lysergic acid diethylamide, 573
Fine, Harold J., 435
Finesinger, Jacob Ellis, 415
Fischgold, H., 583
Fisher, Charles, 315
Flach, Frederic F., 171
Ford, Donald H., 530
Forer, Bertram R., 83
Forgetting narrative material, rate and mode of in Korsakoff patients, 391
Formation and extinction of conditioned reflexes in brain-damaged and mongoloid children, 162
Fortunate Strangers: An Experience in Group Psychotherapy, 501
Free Associations, 503
Freeman, Harry, 62
Freud, Sigmund, 412
Freudian theory, methodological study of:
  I. Basic concepts, 11
  II. The libido theory, 133
  III. Narcissism, bisexuality and the dual instinct theory, 207
  IV. Structural hypothese, problem of anxiety, and post-Freudian ego psychology, 341
Friedman, Irving, 296
Functional and morphological alterations in CNS resulting from irradiation, 512

Further remarks on porphyria and report of prolonged observation of a case, 296
Fuster, Joaquin M., 252

G

Galt, William E., 312
Garfield, Sol L., 492
Garmezy, Norman, 450
Genie, Irrsinn und Ruhm, 4th ed., 308
Glad, Donald D., 506
Glick, Burton S., 20
Globus pallidus, depth stimulation and recording in and in thalamus with paralysis agitans patients, 417
Glycosuria, severe renal, association of psychosis with, 196
Glyoxylic acid test for schizophrenia: observations in two hospitals, 581
Gibby, Robert G., 99
Goldman, Alfred E., 568
Gordon, H. L., 590
Gottleib, Jacques S., 486
Grad, B., 69
Greifenstein, F., 54
Greenfield, J. G., 204
Griffith, E. Clay, 564
Guilt and shame in torticollis, 154
Guilty and the Innocent, The, 507
Gurdjian, E. S., 273

H

Haley, Jay, 357
Hallucinogenic effects of brief sensory isolation, 486
Hands, feet and lips, contactual responses of in congenital bilateral athetosis, 117
Hanlon, Thomas E., 95
Hardy, W. G., 273
Herskovitz, Herbert H., 467
Heterogeneity in schizophrenia, implications of premorbid adjustment and performance in interpreting, 450
Hexafluorodiethyl ether (Indoklon®)
and electroconvulsive therapy, comparative study, 95
availability of by intravenous injection as a convulsant in psychiatric treatment, 92
Higher socio-economic groups, anti-social behavior of adolescents from, 467
Hirano, Asao, 35
History of Neurology A, 202
Hoagland, Hudson, 62
Hobbs, G. E., 581
Homosexual panic: Clinical and theoretical considerations, 20
Hostility score in torticollis, 153
Hunzinger, W., 69
Hutt, Max L., 99
5-hydroxyindole acetic acid and blood and urinary serotonin levels in schizophrenic and normal subjects, 62

I

I^{131}-labelled triiodothyronine, relationship of rat blood brain barrier to, 530
Images and dreams, influence of subliminal visual stimulation on, 315
Implications of premorbid adjustment and performance for interpreting heterogeneity in schizophrenia, 450
Indoklon® (hexafluorodiethyl ether)
and electroconvulsive therapy, comparative study, 95
availability of by intravenous injection as a convulsant in psychiatric treatment, 92
Infant motor responses, relation to of congenital bilateral athetosis, 127
Influence of chlorpromazine on pathologic emotions and sexual unrest, 171
Influence of subliminal visual stimulation on subsequent images and dreams, 315
Instinct (dual theory), narcissism, bisexuality and, 207
Institutions, pro and con, 389
Integration and development, schizophrenic, stages of, 429
autistic, 432
empathic, 429
parataxic, 431
prototaxic, 430
syntaxic, 433
Integration and differentiation in schizophrenia, 542
Interdisciplinary communication, psychological report as a problem in, 86
Internal carotid, supraclinoid portion of, and middle cerebral arteries, ruptured aneurysms of, 35
Interpreting heterogeneity in schizophrenia, implications of premorbid adjustment and performance in, 450
Interview, diagnostic psychiatric, and test situation, different levels of sampling behavior in, 81
Intravenous injection, availability of hexafluorodiethyl ether by as a convulsant in psychiatric treatment, 92
Intravenous route, cyanide encephalopathy produced by, 302
Intrusion by technology and automation into families, 387
Ionizing radiations, review of Soviet research on central nervous system effects of, 511
Irradiation, *see radiation*

Isolation, old-age, battle against, 389
Isolation, sensory: Hallucinogenic effects, 486
Israel, L., 313

J

Jackson, Don D., 375
Jahoda, Marie, 504
Jones, Ernest, 503
Jones, Harry, 291
Jones, Marshall R., 102
Judah, Leopold N., 198

K

Kantor, Robert E., 429
Kardiner, Abram, 11, 133, 207, 341
Karush, Aaron, 11, 133, 207, 341
Kempf's concept of homosexual panic, 23
Kessler, Charles R., 193
Klopfer, Walter G., 86
Klotz, H. P., 313
Knupfer, Genevieve, 375
Korsakoff's psychosis, rate and mode of forgetting narrative material in, 391
Kral, V. A., 69
Krantz, John C., 92, 95, 306
Krieger, George, 375
Kurland, Albert A., 92, 95

L

Labyrinthine responses in congenital bilateral athetosis, 116
Lange-Eichbaum, Wilhelm, 308
Lateralized brain lesions, differential effects of on Trail Making Test, 257
Leadership, in family of the schizophrenic, 366
Learning, verbal, reminiscence of in schizophrenia, 457
Lesions, lateralized, of brain, differential effects of on Trail Making Test, 257
Levels of blood and urinary serotonin and 5-hydroxyindole acetic acid in schizophrenic and normal subjects, 62
Levine, Murray, 467
Levine, Seymour, 302
Lewis, Jerry M., 564
Libido theory (in Methodological study of Freudian theory), 133
Lichtenberg, Joseph D., 243
Lindner, D. W., 273
Ling, Alfred S. C., 92
Lips, hands and feet, contactual responses of in congenital bilateral athetosis, 117
Loathsome Women, 201
Looking, act of, in torticollis, 155
Lovegrove, T. D., 581
Lumbar puncture in cerebrovascular patients, 289
Lumbroso, P., 313
Lysergic acid and its effects on visual discrimination in monkeys, 252
Lysergic acid diethylamide, case of fetishism treated with, 573

M

Management of manic phase of manic depressive psychosis, theoretical and practical considerations of, 243
Manchey, L. Lavan, 92
Manic depressive psychosis, theoretical and practical considerations of management of manic phase of, 243
Manic patient
is psychotic, 243
is selectively defensive, 246
personality defenses of, 245
Mannerisms of Speech and Gestures in Everyday Life, 309
Man's World of Sound, 203
Masserman, Jules, 409
Mathis, P., 583
McMenemy, W. H., 204
Meduna, L. J., 100
Meerloo, Joost A. M., 385
Menstruation as valued function, in female castration complex, 235
Mental disease, evaluation of therapeutic use of trifluprom azine in, 184
Mental phenomena, unexplained, regarding suicide, some explanations for, 578
Mentally Retarded Patient, The, 308
Meprobamate, phenaglycodol and, comparative effects of on anxiety reaction, 193
Mercer, J. D., 405
Mescaline, metabolism of, with note on correlations between metabolism and psychological effects, 177
Metabolism
of mescaline, with note on correlations between metabolism and psychological effects, 177
porphyria, acute intermittent, psychopathology of, 291
Methodological study of Freudian theory:
I. Basic concepts, 11
II. The libido theory, 133
III. Narcissism, bisexuality and the dual instinct theory, 207
IV. Structural hypothesis, problem of anxiety, and post-Freudian ego psychology, 341
Metrazol convulsive therapy modified by succinylcholine, 198
Mette, G., 313
Mettler, Fred A., 551
Meyer, A., 204
Meyer, John S., 54
Michal-Smith, Harold, 308

Middle cerebral arteries and supraclinoid portion of internal carotid, ruptured aneurysms of, 35
Midelfort, C. F., 201
Mind of the Murderer, The, 306
Mittelmann, Bela, 81
Mode and rate of forgetting narrative material in Korsakoff patients, 391
Model system: Family of the schizophrenic, 357
Modern Sociological Theory in Continuity and Change, 306
Mokrasch, L. C., 177
Mongoloid and brain-damaged children, formation and extinction of conditioned reflexes in, 162
Monkeys, effects on visual discrimination of lysergic acid, 252
Monozygotic twins, factors associated with concordance and discordance in schizophrenia in, 1
Morphological and functional alterations in CNS resulting from irradiation, 512
Moser, U., 499
Mother, ambivalent, separation from, 388
Motor deficit in congenital bilateral athetosis, 105
general description, 106
voluntary movement, 123
Motor responses, infant, relation to of congenital bilateral athetosis, 127
Mowrer, O. Hobart, 222
Movements, associated and mass, in congenital bilateral athetosis, 125
Multidimensional (Lorr) scale for psychiatric ratings and triflupromazine, 187
Murphree, Oddist D., 198

N

Narcissism, bisexuality and the dual instinct theory (in Methodological study of Freudian theory), 207
Narrative material, rate and mode of forgetting in Korsakoff patients, 391
Nebraska Symposium on Motivation, 1958, 102
Neck symbolism in torticollis, 153
Nemesis, concept of in psychoneurosis, 29
Neurological Basis of Behavior, 508
Neurological, electroencephalographic and pharmalogical effects of Sernyl (new drug causing symptoms of sensory deprivation), 54
Neuropathology, 204
Neurosurgical diagnostic evaluation of patient with cerebrovascular disease (stroke syndrome), 273
Neustatter, W. Lindesay, 306
New Chemotherapy in Mental Illness, The, 590
New drug causing symptoms of sensory deprivation (Sernyl): Neurological, electroencephalographic and pharmalogical effects, 54
Non-differentiated type of schizophrenic patient, 546
Non-integrated type of schizophrenic patient, 543
Norman, R. M., 204
Nurse-Patient Relationships in Psychiatry, 2nd ed., 205

O

Obnubilations, Comas et Stupeurs: Etudes Electroencephalographiques, 583
O'Connor, C. M., 508
Old-age isolation, battle against, 389
On the motor deficit in congenital bilateral athetosis, 105
Operational Values in Psychotherapy, 506
Ophthalmodynamometry in cerebrovascular patients, 276
Oppenheim, D. E., 412
Orality, schizophrenia and: Studies in abstraction, 564
Outpatient psychotherapy, an appraisal of duration of stay in, 492
Ovesey, Lionel, 11, 133, 207, 341

P

Panic, homosexual: Clinical and theoretical considerations, 20
Paralysis agitans, depth stimulation and recording in thalamus and globus pallidus of patients with, 417
Parataxic stage of schizophrenic development, 431
Paredes, Alfonso, 291
Parent-patient relationships in schizophrenia, 462
Parkinsonism
and psychiatric disorder, relation between, 551
paralysis agitans patients, depth stimulation and recording in thalamus and globus pallidus of, 417
somato-psychologic studies in, 263
Parnell, R. W., 310
Pathologic emotions and sexual unrest, influence of chlorpromazine on, 171
Patient-parent relationships in schizophrenia, 462
Patterns of Abnormal Behavior, 99
Patterns of diurnal variation of circulating eosinophil counts and salivary Na/K in psychiatric patients, 69
Paul, I. H., 315
Perceptual differentiation and two dimensions of schizophrenia, 435
Perceptual organization study, 437
Performance and adjustment, premorbid, implications of for interpreting heterogeneity in schizophrenia, 450
Personality defenses of manic patient, 245
Personality differences between more and less com-

petent psychotherapists as a function of criteria of competence, 375
Personality dynamics in torticollis, 150
Phallic component of female sexuality, 239
Pharmalogical, neurological and electroencephalographic effects of Sernyl (new drug causing symptoms of sensory deprivation), 54
Phenaglycodol and meprobamate, comparative effects of on anxiety reactions, 193
Phenomena regarding suicide, mental, some explanations for, 578
1-(phenylcyclohexyl) piperidine, monohydrochloride (Sernyl), new drug causing symptoms of sensory deprivation, 54
Physiological factors in adaptive significance of the dream, 144
Pierce, John R., 203
Porphyria, acute intermittent, psychopathology of, 291
Porphyria, further remarks on, and case report, 296
Porteus maze test and triflupromazine, 187
Post-Freudian ego psychology, structural hypothesis, problem of anxiety and, 341
Posture, resting, in congenital bilateral athetosis, 113
Premorbid adjustment and performance, implications of for interpreting heterogeneity in schizophrenia, 450
Problem in interdisciplinary communication, psychological report as a, 86
Process-reactive concept in schizophrenia, development of, 452
Process-reactive continuum, the: A theoretical proposal, 429
Process-reactive distinction, the: Key to problem of schizophrenia? 442
Prototaxic stage of schizophrenic development, 430
Psychiatric disorder, relation between parkinsonism and, 551
Psychiatric ecology, 385
Psychiatric interview, diagnostic, and test situation, different levels of sampling behavior in, 81
Psychiatric patients, diurnal variation patterns of circulating eosinophil counts and salivary Na/K in, 69
Psychiatric treatment, availability of hexafluorodiethyl ether by intravenous injection as a convulsant in, 92
Psychiatrists and psychologists communicating, re psychological tests, 76
Psychiatrist's decision to refer a patient for psychological testing, 88
Psychological effects and metabolism of mescaline, correlations between, 177
Psychological report as a problem in interdisciplinary communication, 86
Psychological studies of Korsakoff's psychosis: IV. Rate and mode of forgetting narrative material, 391
Psychological test reporting: A problem in communication between psychologists and psychiatrists, 76, 77, 81, 83, 86, 88
Psychological test reports: Universal or discriminating, 83
Psychological testing after triflupromazine, 189
Psychological testing, psychiatrist's decision to refer a patient for, 88
Psychologists and psychiatrists communicating, re psychological tests, 76
Psychoneurosis, nemesis, concept of in, 29
Psychopathology of acute intermittent porphyria: Case report, 291
Psychosis
association of with severe renal glycosuria, 196
Korsakoff's, rate and mode of forgetting narrative material in, 391
manic depressive, theoretical and practical considerations of management of manic phase, 243
Psychosomatic
studies, somato-psychologic, in Parkinson's disease, 263
Psychotherapie in der Gegenwart, Die, 590
Psychotherapy
outpatient, an appraisal of duration of stay in, 492
with alcoholics, 477
Psychotic, manic patient is, 243

R

Radiation
ionizing, review of Soviet research on central nervous system effects of, 511
reactions, autonomic nervous system role in, 519
syndrome, acute, CNS role in, 517
Radiation effects
on CNS, morphological and functional, 512
on conditioned reflex responses, 522
Rail-walking test and triflupromazine, 188
Rand, Robert W., 417
Rat blood brain barrier relationship to I^{131}-labelled triiodothyronine, 530
Rate and mode of forgetting narrative material in Korsakoff patients, 391
Raverdy, P., 313
Referral of patient for psychological testing, psychiatrist's decision to, 88
Reflex responses, conditioned, effects of radiation on, 522
Reflexes, conditioned, in brain-damaged and mon-

goloid children, formation and extinction of, 162
Reflexes, tonic-neck, in congenital bilateral athetosis, 114
Regan, Peter F., III, 171
Rehabilitation activities, tranquilizing drugs and, effect of on ward behavior, 568
Reich, Peter, 196
Reitan, Ralph M., 257
Relation between parkinsonism and psychiatric disorder, 551
Relation of phallic to feminine component of female sexuality, 242
Relationship of blood brain barrier of rat to I^{131}-labeled triiodothyronine, 530
Renal glycosuria, severe, association of psychosis with, 196
Render, Helena W., 205
Reminiscence in verbal learning in schizophrenia, 457
Reporting of psychological tests: A problem in psychologists-psychiatrists communication, 76
Research, Soviet, on central nervous system effects of ionizing radiation, review of, 511
Resistance to passive movement in congenital bilateral athetosis, 117, 126
Responses, conditioned reflex, effects of radiation on, 522
Review of Soviet research on central nervous system effects of ionizing radiation, 511
Riedel, Albert F., 564
Riese, Walther, 202
Riklan, Manuel, 263
Rodnick, Eliot H., 450
Roebuck, Basil E., 184
Rosenbaum, Gerald, 486
Rosenthal, David, 1
Roth, Nathan, 296
Rules in family of the schizophrenic, 363
Ruptured aneurysms of supraclinoid portion of internal carotid and middle cerebral arteries, 35

S

Sakel, Manfred, 505
Sampling behavior, different levels of in diagnostic psychiatric interview and test situation, 81
Schizophrenia: A Review of the Syndrome, 206
Schizophrenia
and orality: Studies in abstraction, 564
as a dichotomous typology, 451
diagnostic criteria, methodological problems in, 453
glyoxylic acid test for, 581
in monozygotic twins, factors associated with concordance and discordance, 1
integration and differentiation in, 542
perceptual differentiation and two dimensions of, 435
premorbid adjustment and performance, implications of for interpreting heterogeneity in, 450
process-reactive concept, development of, 452
process-reactive distinction the key to? 442
serotonin, blood and urinary, and 5-hydroxyindole acetic acid levels in normal and schizophrenic subjects, 62
Schizophrenia studies
censure, significance of in, 460
patient-parent relationships in, 462
reminiscence, verbal learning, 457
visual discrimination in, 455
Schizophrenic integration and development, stages of, 429
autistic, 432
empathic, 429
parataxic, 431
prototaxic, 430
syntaxic, 433
Schizophrenic patient
different behavior of, 367
family of, a model system, 357
non-differentiated type, 546
non-integrated type, 543
Science and Psychoanalysis, 409
Search for Man's Sanity, A, 312
Searles, Harold F., 542
Self Destruction, 101
Selye, Hans, 309
Sensory deprivation, new drug causing symptoms of (Sernyl), 54
Sensory isolation: Hallucinogenic effects of a brief procedure, 486
Separation from the ambivalent mother, 388
Sernyl (1-(phenylcyclohexyl) piperidine, monohydrochloride), new drug causing symptoms of sensory deprivation, 54
Serotonin, blood and urinary, and 5-hydroxyindole acetic acid levels in schizophrenic and normal subjects, 62
Sexual desire and femininity, fears of loss of in female castration complex, 236
Sexual unrest and pathologic emotions, influence of chlorpromazine on, 171
Sexuality, female
feminine component of, 238
phallic component of, 239
Shame, guilt and, in torticollis, 154
Sheets, Carolyn S., 95
Side effects of trifluprom azine, 186
Significance, adaptive, of the dream, 144
Silber, Austin, 477
Simmons, Belvin A., 564

Socio-economic groups, higher, anti-social behavior of adolescents from, 467
Somato-psychologic studies in Parkinson's disease, 263
Some explanations for unexplained mental phenomena regarding suicide, 578
Some factors associated with concordance and discordance with respect to schizophrenia in monozygotic twins, 1
Soviet research on central nervous system effects of ionizing radiation, review of, 511
Spivack, George, 467
Stahl, Walter R., 511
Star tracing test and triflupromazine, 188
Star Wormwood, 584
Stay in outpatient psychotherapy, an appraisal of duration of, 492
Stein, Leopold, 201
Stekel, Boisen and others' alternative view of the unconscious, 224
Stern, Erich, 590
Stevenson, Ian, 177
Stimulation and recording, depth, in thalamus and globus pallidus of patients with paralysis agitans, 417
Stimulation, subliminal visual: Influence on subsequent images and dreams, 315
Stroke syndrome (cerebrovascular disease) patient, neurosurgical diagnostic evaluation of, 273
Structural hypothesis, problem of anxiety, and post-Freudian ego psychology, 341
Studies in abstraction: Schizophrenia and orality: Preliminary results, 564
Subliminal visual stimulation: Influence on subsequent images and dreams, 315
Succinylcholine, metrazol convulsive therapy modified by, 198
Suicide, some explanations for unexplained mental phenomena regarding, 578
Supraclinoid portion of internal carotid and middle cerebral arteries, ruptured aneurysms of, 35
Syntaxic stage of schizophrenic development, 433
Szondi, L., 499
Szondi Test in Diagnosis, Prognosis and Treatment, The, 499

T

Talland, George A., 391
Tarshes, Elaine L., 257
Technology and automation, intrusion of into families, 387
Test situation and diagnostic psychiatric interview, different levels of sampling behavior in, 81
Test, Trail Making, differential effects of lateralized brain lesions on, 257
Tetanie Chronique ou Spasmophilie, La, 31
Thalamus and globus pallidus, depth stimulation and recording in, with patients with paralysis agitans, 417
Theoretical and clinical considerations of homosexual panic, 2
Theoretical and practical considerations of management of manic phase of manic depressive psychosis, 243
Therapeutic use of triflupromazine in mental disease, evaluation of, 184
Therapy, electroconvulsive, and hexafluorodiethyl ether (Indoklon®), comparative study of, 95
They Walk in Shadow, 405
Three-person system in family of the schizophrenic, 361
Time and age, in torticollis patients, 155
Tomsich, Rosa, 296
Tonic-neck reflexes in congenital bilateral athetosis, 114
Torticollis
  and looking, 155
  and time and age, 155
  body image in, 152
  guilt and shame in, 154
  hostility score in, 153
  neck symbolism in, 153
  personality dynamics in, 150
Trail Making Test, differential effects of lateralized brain lesions on, 257
Tranquilizing drugs and rehabilitation activities, effect of on ward behavior, 568
Transitional consciousness in adaptive significance of the dream, 145
Triflupromazine
  and apparent motion discrimination test, 187
  and body sway test, 188
  and dot judgment test, 188
  and multidimentional (Lorr) scale for psychiatric ratings, 187
  and Porteus maze test, 187
  and star tracing test, 188
  and rail-walking test, 188
  evaluation of therapeutic use of in mental disease, 184
  psychological testing after, 189
  side effects, 186
Triiodothyronine, I^{131}-labelled, relationship of rat blood brain barrier to, 530
Truitt, Edward B., Jr., 92
Twins, monozygotic, factors associated with concordance and discordance in schizophrenia in, 1
Twitchell, Thomas E., 105

Two dimensions of schizophrenia, perceptual differentiation and, 435

U

Ullman, Montague, 144
Unconscious
alternative view of Stekel, Boisen and others, 224
changing conceptions of, 222
re-examined in a religious context, 227
Unexplained mental phenomena regarding suicide, some explanations for, 578
Universal or discriminating: Psychological test reports, 83
Urinary and blood serotonin and 5-hydroxyindole acetic acid levels in schizophrenic and normal subjects, 62
Urine analysis in correlation of mescaline metabolism and psychological effects, 179
Urine, glyoxylic acid test of for schizophrenia, 581

V

Variation, diurnal, in patterns of circulating eosinophil counts and salivary Na/K in psychiatric patients, 69
Ventriculo-encephalography in cerebrovascular patients, 289
Verbal learning, reminiscence of in schizophrenia, 457
Visual discrimination
in monkeys, effects of lysergic acid on, 252
in schizophrenia, 455
Visual stimulation, subliminal: Influence on subsequent images and dreams, 315

W

Walter, Richard D., 417
Walton, Alan Hull, 508
Ward behavior, effect of tranquilizing drugs and rehabilitation activities on, 568
Webb, M. W., 499
Webster, J. E., 273
Weiner, Herman, 263
Weiss, Olga M., 205
Wenk, Eugene J., 302
Williams, Elizabeth, 184
Winder, C. L., 429
Whitelaw, J. D. A., 573
Wolstenholme, G. E. W., 508
Wurtz, Kenneth R., 578

Y

Young Man Luther, 406

Z

Zamansky, Harold S., 568
Zimet, Carl N., 435
Zimmerman, H. M., 35
Zukin, Paul, 193

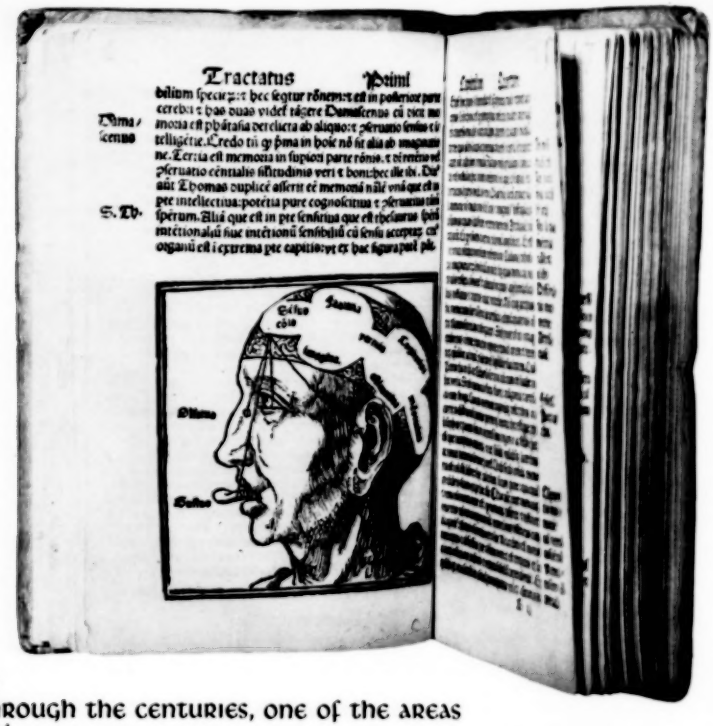
DOES NOT CIRCULATE

Volume 129 · Number 6 · December 1959

THE UNIVERSITY
OF MICHIGAN
JAN 26 1960
MEDICAL
LIBRARY

Published monthly by

THE WILLIAMS & WILKINS COMPANY



Through the centuries, one of the areas most inaccessible to treatment has been depression.

For the modern treatment of depression
A new drug from Pfizer research

NIAMID® *a specific for depression*

brand of nialamide

When NIAMID is used as an adjunct to psychiatric procedures, patients become more accessible and more manageable.

- Clinically effective in a broad range of depressive syndromes.
- Frequently effective in regressed patients in whom other therapy has failed.
- Favorable behavioral changes reduce the need for electroshock therapy.
- A high degree of safety already proved in several thousand patients — NIAMID has not been reported to cause jaundice, agranulocytosis, Parkinson-like extrapyramidal symptoms or visual disturbances, and hypotensive effects have rarely been noted.
- Side effects are infrequent and mild, and often lessened or eliminated by a reduction in dosage; NIAMID acts slowly, without rapid jarring of physical or mental processes.

Already clinically proved in several thousand patients—

NIAMID is available as 25 mg. and 100 mg. tablets; complete references, literature and additional professional information may be obtained from the Medical Department, Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

Pfizer *Science for the world's well-being™*

Published monthly by The Williams & Wilkins Co., 428 E. Preston St., Baltimore 2, Md., U. S. A.
Subscription price $15.00, single issue $1.50 Second-class postage paid at Baltimore, Md.

Table of Contents

A REVIEW OF SOVIET RESEARCH ON THE CENTRAL NERVOUS SYSTEM EFFECTS OF IONIZING RADIATIONS. *Walter R. Stahl* 511

THE RELATIONSHIP OF THE BLOOD BARRIER OF THE RAT TO I^{131}-LABELLED TRIIODOTHYRONINE. *Donald H. Ford* 530

INTEGRATION AND DIFFERENTIATION IN SCHIZOPHRENIA. *Harold F. Searles* 542

RELATION BETWEEN PARKINSONISM AND PSYCHIATRIC DISORDER. *Fred A. Mettler and Archie Crandell* 551

STUDIES IN ABSTRACTION: SCHIZOPHRENICS AND ORALITY: PRELIMINARY RESULTS. *Jerry M. Lewis, E. Clay Griffith, Albert E. Riedel and Belvin A. Simmons* 564

THE EFFECT OF TRANQUILIZING DRUGS AND REHABILITATION ACTIVITIES ON WARD BEHAVIOR. *Alfred E. Goldman and Harold S. Zamansky* 568

A CASE OF FETISHISM TREATED WITH LYSERGIC ACID DIETHYLAMIDE. *J. D. A. Whitelaw* 573

BRIEF COMMUNICATIONS.

Kenneth R. Wurtz 578

T. D. Lovegrove, J. B. Derrick, C. W. Buck and G. E. Hobbs 581

BOOK REVIEWS 583

INDEX 593

Information for Authors

Manuscripts and correspondence pertaining thereto should be addressed to the Managing Editor: DR. H. A. ROBINSON, The Psychiatric Institute, University of Maryland. Baltimore 1, Maryland.

Manuscripts should be typed double spaced on one side only of 8½ x 11 paper. The original and one clearly legible carbon copy should be submitted.

It is helpful if the author supplies a short title for use as a running head. This should be typed on a separate sheet and be the first page of manuscript. Type the complete title of the article on a second sheet, and the authors' names and affiliations on a third sheet. Type double-spaced on separate sheets: tabular matter, case histories, quotations, formulas, and other subsidiary matter in the text, footnotes, bibliographies, and legends for illustrations. Legends must not be attached to or written on the illustration copy. Positions for tables and figures in the text should be indicated in the margin of the text page.

Manuscripts should be accompanied by two copies of an abstract of 300 words or less

Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. The title of the article, name of author, and number of the figure should be written with a soft pencil on the back of each illustration, and the top designated.

References should be designated in the text by number in parentheses, e.g., (7). The list headed REFERENCES at the end of the paper should be arranged in alphabetical order and numbered. Abbreviations should follow the style of the Quarterly Cumulative Index Medicus. Examples:

Book reference:

3. CRITCHLEY, M. *The Parietal Lobes.* pp. 171–181. Edward Arnold & Co., London, 1953.

Journal reference:

11. ROSVOLD, H. E., MIRSKY, A. F. AND PRIBRAM, K. H. Influence of amygdalectomy on social behavior in monkeys. J. Comp. & Physiol. Psychol., **47:** 173–178, 1954.

Authors will be charged for alterations in proof in excess of 10 per cent of the original cost of composition and for the cost of engravings in excess of $50.00. One invoice will be sent covering cost of reprints, alterations and engravings.

The editorial office should be notified promptly of any change of address.

Galley proofs are sent to the author, and should be returned with manuscript to the editorial office. A table of cost of reprints, with an order slip, is sent with galley proof.

The Journal of
NERVOUS and MENTAL DISEASE

COPYRIGHT© 1960 BY THE WILLIAMS & WILKINS CO.

THE PSYCHIATRIC INSTITUTE • University of Maryland • Baltimore 1, Maryland

JACOB E. FINESINGER, **Editor-in-Chief**
H. A. ROBINSON, **Managing Editor**

EDITORIAL BOARD

ROBERT A. CLEGHORN, *Montreal*
JEROME D. FRANK, *Baltimore*
ROBERT G. GRENELL, *Baltimore*
ROBERT R. HOLT, *New York*
JAMES L. O'LEARY, *St. Louis*
TALCOTT PARSONS, *Cambridge*
THOMAS S. SZASZ, *Syracuse*

ADVISORY BOARD

RAYMOND D. ADAMS, *Boston*
W. ROSS ASHBY, *Gloucester, England*
PHILIP BARD, *Baltimore*
MANFRED BLEULER, *Burgholzli, Switzerland*
MARY A. B. BRAZIER, *Boston*
JEAN DELAY, *Paris, France*
JOEL ELKES, *Bethesda*
ANGEL GARMA, *Buenos Aires, Argentina*
WENDELL R. GARNER, *Baltimore*
MARIO GOZZANO, *Rome, Italy*
MANFRED S. GUTTMACHER, *Baltimore*
D. O. HEBB, *Montreal*
ERNEST R. HILGARD, *Stanford*
HANS HOFF, *Vienna, Austria*
MAXWELL JONES, *Sutton, England*
MAURICE LEVINE, *Cincinnati*
NOLAN D. C. LEWIS, *Princeton*
A. H. MASLOW, *Waltham*
JEROME K. MERLIS, *Baltimore*
C. J. MUNCH-PETERSEN, *Aarhus, Denmark*
J. H. QUASTEL, *Montreal*
JOHN R. REID, *Baltimore*
DAVID RIESMAN JR., *Chicago*
A. EARL WALKER, *Baltimore*
J. R. WITTENBORN, *New Brunswick*

controls
the acute
psychotic episode

elicits continuing
cooperation

promotes
accessibility

LITERATURE SUPPLIED ON REQUEST

Sparine®

HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

INJECTION TABLETS SYRUP

References: 1. Frain, M.K.: J. Nerv. & Ment. Dis. *125*:529 (Oct.-Dec.) 1957. 2. Graffeo, A.J.: New York State J. Med. *58*:2056 (June 15) 1959. 3. Lesse, S.: Am. J. Psychiat. *113*:984 (May) 1957.

Wyeth Laboratories, Philadelphia 1, Pa.

100 ANNIVERSARY 1860 Wyeth

A Century of Service to Medicine

Tofrānil® a thymoleptic

brand of imipramine HCl

Specific in Depression

does

Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe as in mild cases

Achieve therapeutic benefit with minimal risk of serious side reaction

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofrānil (brand of imipramine HCl) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

.....not a MAO inhibitor

does not

Inhibit monoamine oxidase either in brain or liver with its associated risks

Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

Geigy

13759

Geigy, Ardsley, New York

LIFT THE DEPRESSION

Lift the depression with Marplan. Therapeutically, Marplan is a new, more active amine oxidase regulator. Clinically, it is safer. Medically, it represents a major breakthrough in the chemotherapy of depression. Marplan has been evaluated by some 300 investigators who reported its use in more than 4000 patients. Results have been impressive—frequently dramatic, and side effects have been markedly fewer and less severe. Indications range from moderate to severe psychiatric disorders with associated symptoms of depression, withdrawal or regression. Marplan is also valuable as an adjunct in psychotherapy to facilitate the patient's responsiveness. *Complete literature* giving dosage, side effects and precautions is available upon request and should be consulted before prescribing.

Supplied: 10-mg tablets in bottles of 100 and 1000.

Bibliography: **1.** H. F. Darling, W. Kruse, G. F. Hess and M. G. Hoermann, *Dis. Nerv. System, 20*:269, 1959. **2.** W. B. Abrams, A. Bernstein, V. D. Mattia, Jr., R. J. Floody and L. O. Randall, Scientific Exhibit, American Medical Association Meeting, Atlantic City, N. J., June 8-12, 1959. **3.** Reports on file in the Department of Pharmacology, Roche Laboratories. **4.** Clinical reports on file, Roche Laboratories. **5.** L. O. Randall and R. E. Bagdon, *Dis. Nerv. System, 19*:539, 1958. **6.** W. Hollander and R. W. Wilkinson, in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. **7.** R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. **8.** I. Kimbell, paper read at Cooperative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959. **9.** L. Alexander and S. R. Lipsett, *Dis. Nerv. System, 20*(Suppl.):26, 1959. **10.** A. L. Scherbel and J. W. Harrison, *Ann. New York Acad. Sc., 80*:(3), 820, Sept. 17, 1959. **11.** S. L. Cole, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. **12.** L. O. Randall and R. E. Bagdon, Second Marsilid Symposium, Chicago, Ill., May 8, 1958. **13.** O. Resnick, *Ann. New York Acad. Sc., 80*:(3), 726, Sept. 17, 1959. **14.** G. Zbinden and A. Studer, *ibid.*, p. 873. **15.** T. R. Robie, *Dis. Nerv. System, 20*:182, 1959.

MARPLAN T.M.—1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine ROCHE®

Marplan

achieves a happy balance of potency/safety

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc. Nutley 10, N. J.

remove
the
depression

with
new

Nardil

brand of phenelzine dihydrogen sulfate

a true antidepressant

Nardil

rapidly effective—antidepressant response often within a few days; complete remission usually within 2 to 6 weeks, in 4 out of 5 patients.[1-5]

low toxicity—no significant reports of toxicity to liver, blood or kidneys; side effects only occasional or mild in 3 years of exacting clinical trial and in thousands of cases to date.[1-4]

corrective—helps remove the depression, rather than merely masking the symptoms... this well tolerated yet potent monoamine oxidase inhibitor passes the blood-brain barrier rapidly with preferential distribution to the brain—not the liver ...restores the mild-to-deeply depressed or suicidal patient without institutionalization and without recourse to ECT in most cases.[1-4]

simple dosage schedule—1 tablet 3 times a day.

Indications: For the office or hospital treatment of mild to severe depressions, endogenous or reactive, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis. Improves the depressed phase of affective (manic-depressive) psychosis, and relieves the depression of catatonic schizophrenics, although not affecting the psychosis *per se*.

Side Effects: Occasionally postural hypotension is seen, particularly in those patients whose pretreatment pressure is low. Infrequently reported nausea, ankle edema, delayed micturition or constipation is managed by appropriate adjunctive therapy, or will abate when dosage is reduced to maintenance level.

Dosage: One tablet three times a day.

Maintain until remission of symptoms, which may require 2-6 weeks; then reduce to a maintenance level of 1 or 2 tablets a day. For the occasional patient who does not respond to the above starting dose, an additional one or two 15 mg. tablets may be given at bedtime.

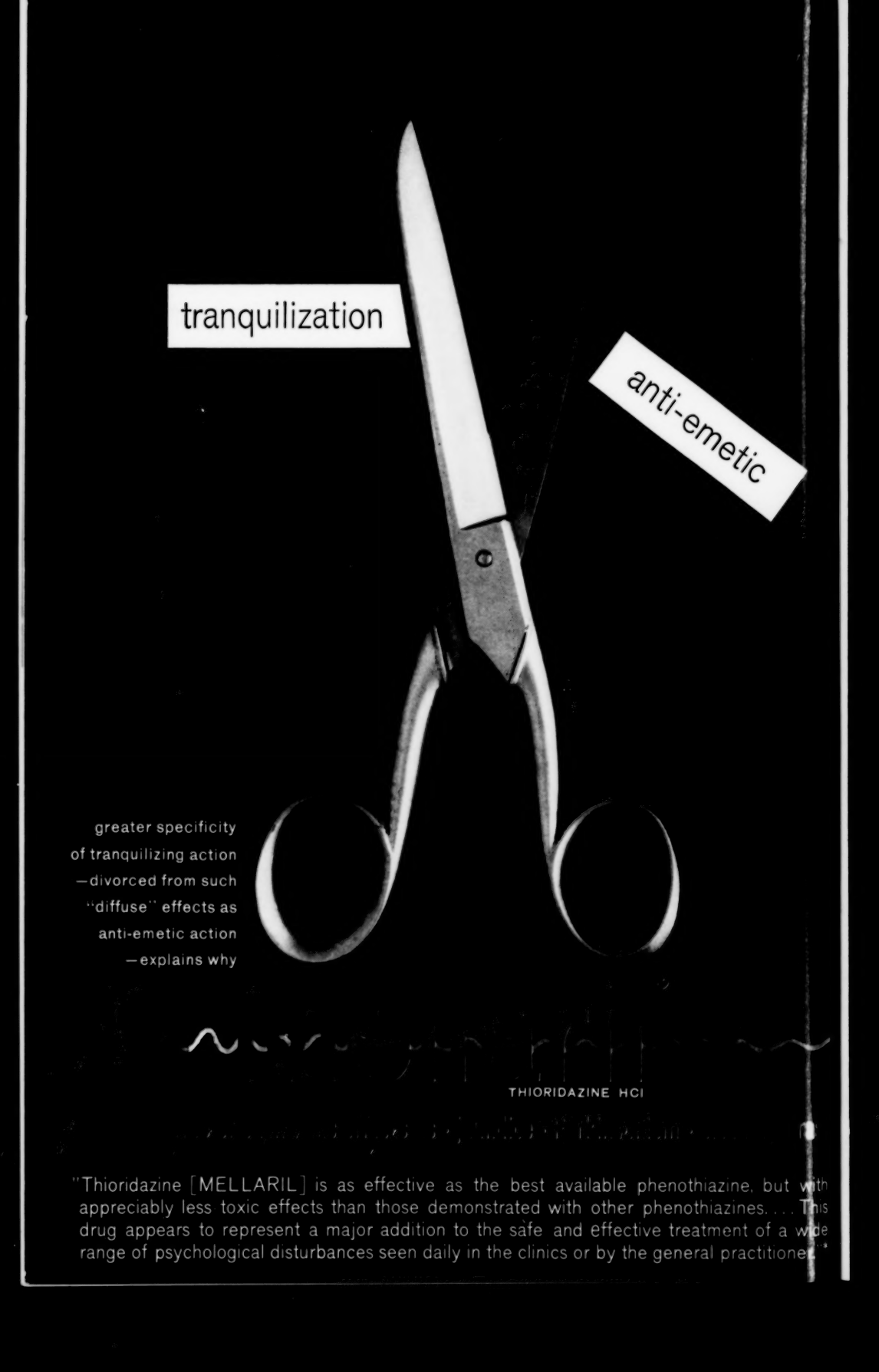
Supplied: Orange-coated tablets, each containing 15 mg. of phenylethylhydrazine present as the dihydrogen sulfate. Bottles of 100.

Caution: Even though there have been no significant reports of toxic effects on the liver with the use of Nardil, as a matter of caution patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be under close medical supervision.

references: **1.** Sains, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* 116:71 (July) 1959. **4.** Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med.*, 6:1573 (Sept.) 1959. **5.** Dickel, H. A.; Dixon, H. H.; Shanklin, J. G., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med.*, 6:1579 (Sept.) 1959.

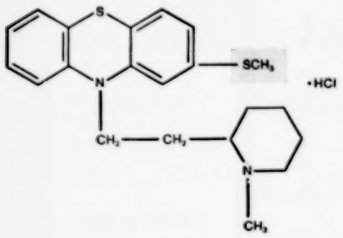
WARNER CHILCOTT

MORRIS PLAINS, N.J.



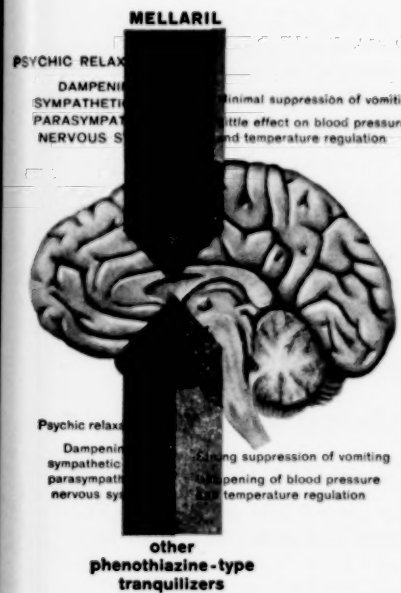
"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

a new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical (S-CH_3) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.



2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.

3 A notable absence of extrapyramidal stimulation.

4 Lack of impairment of patient's normal drive and energy.

5 Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.

Indication	Usual Starting Dose	Total Daily Dosage Range
ADULTS: Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

Mellaril Tablets, 10 mg., 25 mg., 100 mg.

*Ottfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

SANDOZ

SEDATION
AND EUPHORIA FOR NERVOUS, IRRITABLE PATIENTS

Use
VALERIANETS-DISPERT
Reg. U. S. Pat. Off.

Each Chocolate Coated Tablet Contains Ext. Valerian (highly concentrated) 0.05 Gm. dispergentized finely subdivided for maximum efficiency
TASTELESS, ODORLESS, NON-DEPRESSANT SEDATIVE and EUPHORIC
VALERIANETS-DISPERT are indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia.

Dose: 1 or 2 tablets t.i.d. — Bottle of 50 and of 100 tablets
At All Prescription Pharmacies

STANDARD PHARMACEUTICAL CO. INC. • 253 West 26th St. New York 1, N. Y.

For Intestinal Dysfunction
NUCARPON®
Each tablet cont: Extract of Rhubarb, Senna, Precip. Sulfur, Peppermint Oil, Fennel Oil in activated charcoal base.

For making Burow's Solution U.S.P. XIV
WET DRESSING Use
PRESTO-BORO®
(Aluminum Sulfate and Calcium Acetate)
POWDER IN ENVELOPES — TABLETS —
For treatment of Swellings, Inflammations, Sprains

For Pulmonary Conditions
TRANSPULMIN®
3% solution Quinine with 2½% Camphor for intramuscular injection.

Garma: PEPTIC ULCER AND PSYCHOANALYSIS

"... Primarily concerned with actual clinical case histories and with the examination of material communicated in psychoanalytic sessions. It is the author's thesis that ulcer patients have a dependence through being in love with someone who does not satisfy them genitally; this factor in turn acts more traumatically upon them because they are often people with a professional activity that demands too much of them and which prevents them from discharging the emotional tension of their conflicts. He then attempts to substantiate this thesis by giving detailed case histories."—*Gastroenterol.*

160 pp. • $6.00
By ANGEL GARMA, *M.D.*,
Buenos Aires, Argentina

THE WILLIAMS & WILKINS COMPANY
BALTIMORE 2, MARYLAND, U.S.A.

Information for Subscribers

THE JOURNAL OF NERVOUS AND MENTAL DISEASE

AN EDUCATIONAL JOURNAL OF NEUROPSYCHIATRY • FOUNDED IN 1874

Published monthly, two volumes a year. Subscription price $15.00 per year, $15.50 in Canada, and $16.50 foreign and postal union. Subscriptions should be sent to the publisher.

New subscriptions and renewals are entered to begin with the first issue of the year when subscription is received. Should any issue of that volume be out of print when subscription is received, the pro-rata value will be refunded to the subscriber.

Subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

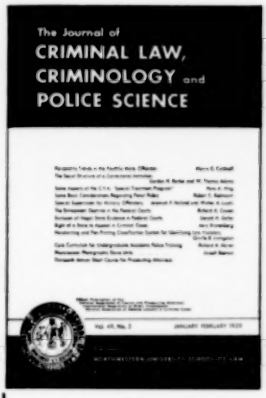
Claims for copies lost in the mails must be received within 30 days (domestic).

Change of address: Publisher must be notified 60 days in advance. Journals undeliverable because of incorrect address will be destroyed. Duplicates can be obtained (if available) from the publisher at the regular price of a single issue ($1.50).

Correspondence concerning business matters should be addressed to the publisher.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals • 428 East Preston Street, Baltimore 2, Md., U.S.A.



The Journal of CRIMINAL LAW, CRIMINOLOGY and POLICE SCIENCE

Official publication of The National District Attorneys Association and The National Association of Defense Lawyers in Criminal Cases

ROBERT H. GAULT and ORDWAY HILTON, *Editors*

Contents of a recent issue:

International Conference on Criminal Law Administration

International Efforts to Control Narcotics.... *Norman Ansley*

Two Myths in the History of Capital Punishment.... *Thorsten Sellin*

Narcointerrogation of a Criminal Suspect.... *Charles E. Sheedy*

Predicting the Population in Institutions for Delinquent Children and Youth. *Arnold M. Rose and George H. Weber*

Automobile Theft.... *Leonard D. Savitz*

The Exclusionary Rule in Operation—A Comparison of Illinois, California and Federal Law.... *Edward Martin Einhorn*

Admissibility of the Nalline Test as Evidence of the Presence of Narcotics. *Edward C. Conrad*

Comparison of Arm-Cuff and Wrist-Cuff Blood Pressure Patterns in Polygraph Charts.... *Norman Ansley*

X-Ray Studies in Establishing Identity and Manner of Death. *Ernest Lachman*

Reproduction of Foot and Tire Tracks by Plaster of Paris Casting. *Rolland L. Soule*

Some Replies to Forensic Queries in Cannabis Identification. *Livio L. Vagnini*

Scientific Training for Cops?.... *A. C. Germann*

Typewriting—Original and Carbon Copies.... *John L. Harris*

Subscription information: Published bimonthly. Subscription price per year: $7.50. Foreign postage: $.75. Canada postage: $.25. Volumes 50 and 51 current in 1960.

THE WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MARYLAND

Because it sustains relief of myasthenia gravis symptoms up to two and one-half times as long as the regular tablet, new MESTINON TIMESPAN often "eliminates the need for sleep interruption to take further medication and leads to better strength in the morning."* For treatment during waking hours, MESTINON TIMESPAN offers greater convenience, prolonged relief on fewer individual doses, and unprecedented freedom from muscarinic side effects.

DOSAGE: 1-6 tablets daily in divided doses p.r.n. In exceptionally severe cases, up to 10 tablets per day may be required.

HOW SUPPLIED: Tablets, 180 mg each — bottle of 100.

* K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959

p-r-o-l-o-n-g-e-d relief in

Schematic drawing of nerve endings in striated muscle tissue. By inhibiting destruction of acetylcholine at this junction, Mestinon acts specifically to reestablish neuromuscular control and relieve symptoms of myasthenia gravis.

MESTINON® BROMIDE
—brand of pyridostigmin bromide
(3-hydroxy-1-methylpyridinium bromide)
TIMESPAN®

MESTINON TIMESPAN

in sustained release tablets—requires fewer individual doses

ROCHE LABORATORIES•Division of Hoffmann-La Roche Inc•Nutley 10, New Jersey

the promise of

PERMITIL®

Fluphenazine dihydrochloride

in everyday office practice

safely controls the "target symptoms" of
emotional stress with the smallest effective dosage
of any neuroleptic* agent (0.25 mg. b.i.d.)

virtually free from side effects at the
recommended dosage level

a significantly wider spectrum of "target symptoms"
is amenable to therapy

onset of action is rapid; duration of effect is prolonged

Neuroleptic "The term 'neuroleptic' implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on affective tension that distinguishes this response from that to hypnotic drugs. The terms 'ataraxics' and 'tranquilizers' are descriptively impressive, but fail to convey what seems psychopharmacologically unique."[1]

the performance of PERMITIL

in everyday office practice

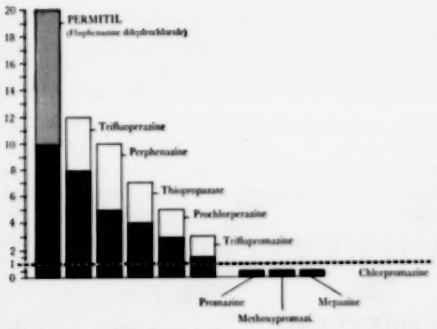
"Fluphenazine (PERMITIL) the latest and most potent phenothiazine tranquilizer was administered from 3 to 20 months to 200 ambulatory and hospitalized patients representing a full spectrum of diagnostic classifications including psychosomatic disorders. Fractional doses of this drug rapidly produced improvement in 74% of these patients while causing a minimum of sedative, autonomic and endocrine effects which disappeared as treatment continued. . . . Patient acceptance of this compound was excellent because its prescription facilitated rather than interfered with the efficient performance of daily tasks. The physician who masters the art of fluphenazine use can treat a widened spectrum of target symptoms safely and

Now,
for the first time,
a phenothiazine
anti-anxiety agent
PERMITIL
designed specifically for
everyday office practice

A Factor to Consider in Phenothiazine Therapy

"The more potent the phenothiazine derivative the fewer the side effects it produces, because less of the chemical is needed to effect behavioral and therapeutic changes."[2]

The Relative Therapeutic Potency of Various Phenothiazines



Adapted from Ayd, F. J., Jr.[3]

Clinical Results with* PERMITIL—*a Phenothiazine. In one study[2] covering a two-year period, PERMITIL was prescribed for 200 patients who were disabled primarily by anxiety and its somatic, emotional, mental and behavioral effects.

"After 3 months of fluphenazine (PERMITIL) therapy, 74% or 148 of the 200 patients evaluated were improved. . . . Thus the therapeutic effectiveness of fluphenazine (PERMITIL) is somewhat better than that of other potent tranquilizers."[2]

The relatively minor somatic reactions occurred in the early weeks of treatment with doses above 2 mg. daily. They seldom required other medication to counteract them and disappeared as the maintenance dose was established. At dosage levels under 3 mg. a day, extrapyramidal side effects were minimal. Results of extensive laboratory tests on 130 patients disclosed that "fluphenazine (PERMITIL) administered over 3 to 18 months had no deleterious effect on the blood, liver or kidney in these patients."[2]

The Importance of* PERMITIL *in Everyday Practice. "In contrast to other phenothiazines, it (PERMITIL) mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."[2]

***How to Prescribe* PERMITIL.** For most adults: One 0.25 mg. tablet b.i.d. (taken morning and afternoon). In refractory cases: Two 0.25 mg. tablets b.i.d. Total daily dosage in refractory cases should not exceed 2 mg., in divided doses. Dosage for children has not been established. *Complete information concerning the use of this drug is available on request.*

Available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J., Jr.: Fluphenazine: its spectrum of therapeutic application and clinical results in psychiatric patients, Current Therapeutic Research, 1:41 (Oct. 15) 1959. 3. Ayd, F. J., Jr.: The current status of major tranquilizers, in press.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

White's

A critical, comprehensive presentation. . .

HANDBOOK OF PHYSIOLOGY

Section 1: Neurophysiology, Volume I

"The American Physiological Society has enlisted the cooperation of physiological scientists from all over the world in attempting to provide a mechanism in this *Handbook of Physiology* series for providing a comprehensive but critical presentation of the state of knowledge in the various fields of functional biology. It is intended to cover the physiological sciences in their entirety once in about ten years, and to repeat the process periodically thereafter."—*From the Foreword*

"Appropriately . . . the *Handbook* begins with a consideration of the nervous system by which the other portions of the body are coordinated and controlled. . . . In contemporary studies of physiological psychology the gap between brain and mind seems most rapidly to be closing; prominent representation of this field is probably the most novel feature of the table of contents of the present Neurophysiology Section."—*From the Preface, Section on Neurophysiology*

CONTENTS: Historical development of neurophysiology (*Mary A. B. Brazier*) • Neuron physiology—introduction (*J. C. Eccles*) • Conduction of the nerve impulse (*Ichiji Tasaki*) • Initiation of impulses at receptors (*J. A. B. Gray*) • Synaptic and ephaptic transmission (*Harry Grundfest*) • Skeletal neuromuscular transmission (*Paul Fatt*) • Autonomic neuroaffector transmission (*U. S. Von Euler*) • Neuromuscular transmission in invertebrates (*E. J. Furshpan*) • Brain potentials and rhythms—introduction (*A. Fessard*) • Identification and analysis of single unit activity in the central nervous system (*Karl Frank*) • Intrinsic rhythms of the brain (*W. Grey Walter*) • The evoked potentials (*Hsiang-Tung Chang*) • Changes associated with forebrain excitation processes: D.C. potentials of the cerebral cortex (*James L. O'Leary & Sidney Goldring*) • Physiopathology of epileptic seizures (*Henri Gastaut & M. Fischer-Williams*) • Sensory mechanisms—introduction (*Lord E. D. Adrian*) • Nonphotic receptors in lower forms (*Hansjochem Autrum*) • Touch and kinesthesis (*Jerzy E. Rose & Vernon B. Mountcastle*) • Thermal sensations (*Yngve Zotterman*) • Pain (*William H. Sweet*) • The sense of taste (*Carl Pfaffman*) • Sense of smell (*W. R. Adey*) • Vestibular mechanisms (*B. E. Gernandt*) • Excitation of auditory receptors (*Hallowell Davis*) • Central auditory mechanisms (*Harlow W. Ades*) • Vision—introduction (*H. D. Hartline*) • Photosensitivity in invertebrates (*Lorus J. Milne & Margery Milne*) • The image-forming mechanism of the eye (*Glenn A. Fry*) • Photoreceptor process in vision (*George Wald*) • Neural activity in the retina (*Ragnar Granit*) • Central mechanisms of vision (*S. Howard Bartley*) • Central control of receptors and sensory transmission systems (*Robert B. Livingston*)

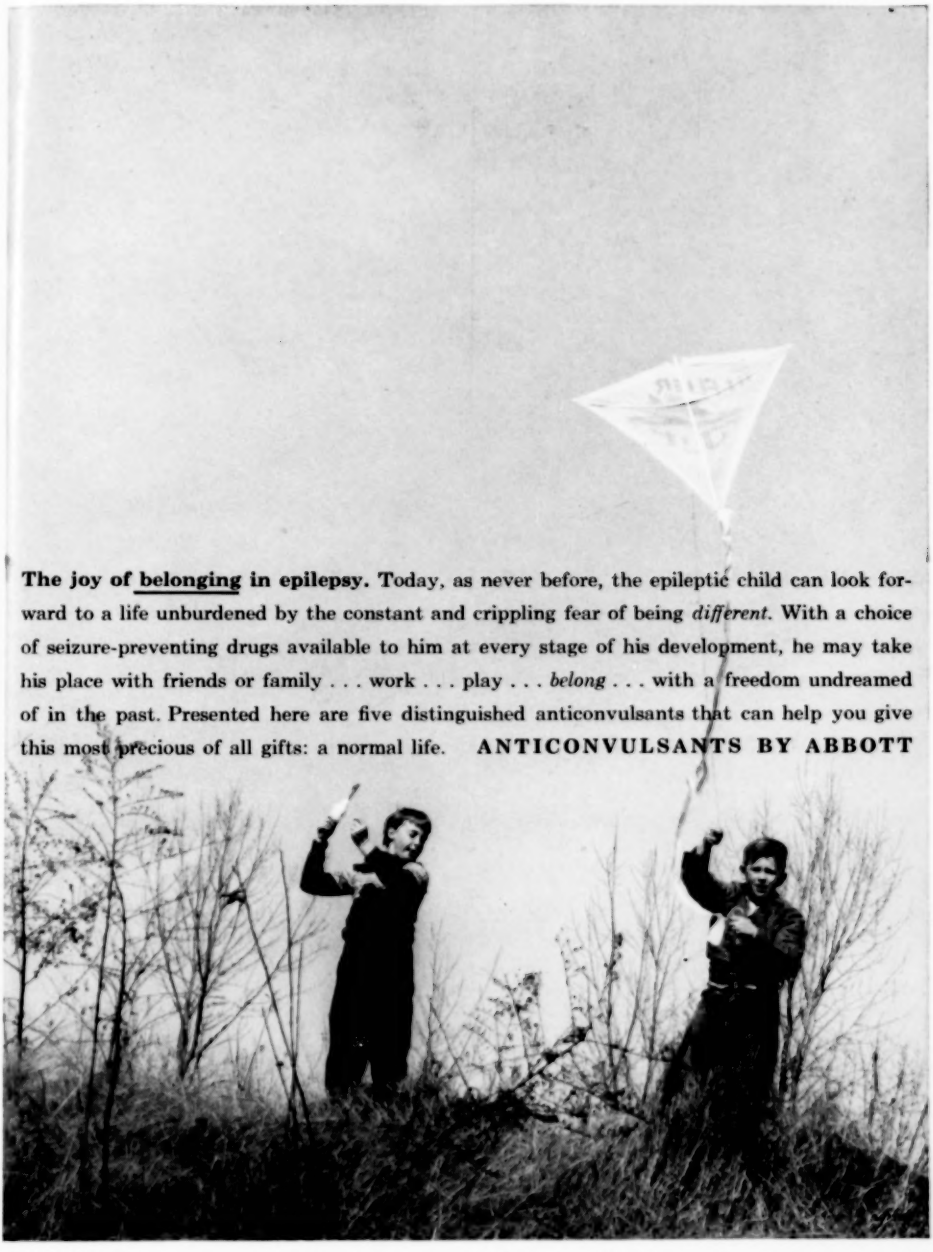
Editor-in-Chief, JOHN FIELD, *Ph.D., Professor of Physiology . . .; Section Editor,* H. W. MAGOUN, *Ph.D., Professor of Anatomy . . .; Executive Editor,* VICTOR E. HALL, *M.D., Professor of Physiology . . .; all of The University of California School of Medicine, Los Angeles. With 35 contributors.*

1959 • *792 pp., 450 figs.* • **$22.00**

Distributed for the American Physiological Society by. . .

THE WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MARYLAND



The joy of belonging in epilepsy. Today, as never before, the epileptic child can look forward to a life unburdened by the constant and crippling fear of being *different*. With a choice of seizure-preventing drugs available to him at every stage of his development, he may take his place with friends or family . . . work . . . play . . . *belong* . . . with a freedom undreamed of in the past. Presented here are five distinguished anticonvulsants that can help you give this most precious of all gifts: a normal life. **ANTICONVULSANTS BY ABBOTT**

PEGANONE® (Ethotoin, Abbott) A hydantoin of exceptionally low toxicity for *grand mal* and psychomotor seizures. **PHENURONE®** (Phenacemide, Abbott) Often effective where other therapy fails in *grand mal, petit mal*, psychomotor and mixed seizures. **GEMONIL®** (Metharbital, Abbott) Relatively non-toxic, for *grand mal, petit mal*, myoclonic and mixed seizures symptomatic of organic brain damage. **TRIDIONE®** (Trimethadione, Abbott) **PARADIONE®** (Paramethodione, Abbott) Homologous agents for symptomatic control of *petit mal*, myoclonic and akinetic seizures. *Literature available on request.*

Many **MIGRAINE** attacks can be **stopped at the start** by the prompt use of...

'MIGRAL'®

Advantage

'MIGRAL' permits maximum ergotamine therapy with the first dose —because the 'MIGRAL' formula includes the proved antiemetic, cyclizine hydrochloride, to counteract the tendency to nausea and vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

In bottles of 20 and 100 tablets.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

8564